STUDY OF MICROALBUMINURIA IN SEPSIS WITH REFERENCE TO APACHE II SCORE

Dissertation submitted to

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APRIL - 2015

CERTIFICATE

This is to certify that the dissertation entitled **"STUDY OF MICROALBUMINURIA IN SEPSIS WITH REFERENCE TO APACHE II SCORE"** is a bonafide work done by **DR.U.PRABAHARAN**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I General Medicine, under our guidance and supervision, during the academic year 2012 - 2015.

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DECLARATION

I, **Dr. U.PRABAHARAN** solemnly declare that dissertation titled **"STUDY OF MICROALBUMINURIA IN SEPSIS WITH REFERENCE TO APACHE II SCORE"** is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 under the guidance and supervision of my unit chief **Prof. R.PENCHALAIAH, M.D.,** Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine**

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LIST OF ABBREVIATIONS

ACR Albumin Creatinine Ratio

AER Albumin Excretion Ratio

AIDS Acquired Immune Deficiency Syndrome

APACHE Acute Physiological and Chronic Health Evaluation

ARDS Acute Respiratory Distress Syndrome

ATP Adenosine Tri Phosphate

bpm Beats Per Minute

CD Cluster Differentiation

CIRCI Critical illness related corticosteroid insufficiency

CMM Cancer Mortality Model

CP Child–Pugh

CRP C-Reactive Protein

DIC Disseminated Intravascular Coagulation

DNA Deoxy Ribonucleic Acid

Fio2 Fraction Of Inhaled Oxygen

GCS Glasgow Coma Scale

HIV Human Immunodeficiency Virus

ICU Intensive Care Unit

IL Interleukin

IM Intra Muscular

INDICAPS Indian Intensive Care Case Mix and Practice Patterns

IRAK IL-1Rc-associated kinase

IV Intravenous

IX Clotting factor 9

LODS Logistic Organ Dysfunction System

LPS Lipopoly Saccharide

mg/dL milli grams per decilitre

MICU Medical Intensive Care Unit

mmol/L milli moles per litre

MODS Multiple Organ Dysfunction Score

MPM Mortality Prediction Model

NEMO nuclear factor B (NF-B

NF B nuclear factor B

PaO2 Partial Pressure Of Oxygen

PCT Procalcitonin

PE Pulmonary Embolism

PIM Paediatric Index of Mortality

PIRO Predisposition- infection-response-organ dysfunction

PP Phosphorylated

RIFLE

Risk, injury, failure, loss and end-stage kidney

classification

RNA Ribo Nucleic Acid

SAH Sub Arachnoid Haemorrhage

SAPS Simplified Acute Physiology Score

sELAM Soluble Endothelial Leukocyte Adhesion Molecules

sICAM soluble InterCellular Adhesion Molecule

SIRS Systemic Inflammatory Response Syndrome

SOFA Sequential Organ Function Assessment

sVCAM soluble Vascular Cell Adhesion Molecule

TAB TAK1-binding protein

TAK transforming growth factor –activating kinase

TIR Toll/IL-1R

TIRAP TIR domain-containing adapter protein

TLR Toll Like Receptor

TNF Tumor Necrosis Factor

VIIIa Clotting Factor 8

X Clotting Factor 10

µg/mg micrograms per milligram

INTRODUCTION

SEPSIS is defined as SIRS (systemic inflammatory response syndrome) that has a proven or suspected microbial etiology. Invasive bacterial infections are the prominent causes of death around the world, particularly among young children. Non-typhoidal *salmonella* species, *Streptococcus pneumonia*, *Haemophilus influenza*, and *Escherichia coli* were the most commonly isolated bacteria.

Sepsis is marked by a severe host defense response that involves triggering of potent inflammatory cascades which release a plethora of pro-inflammatory molecules into the circulation. The endothelium becomes dysfunctional due to the sustained onslaught of the inflammatory molecules and the simultaneous oxidative stress. An early event is the loss of barrier integrity leading to systemic capillary leak. Increased capillary permeability is an early feature of Systemic Inflammatory

CONTENTS

ABSTRACT

Sepsis has very high morbidity and mortality, which leads to major healthcare burden in the world. Though there is far advancement in the therapeutic options, the mortality rate remains high due to the delay in the diagnosis because of lack of availability of reliable diagnostic methods. In sepsis there is potent activation of inflammatory cascade leads to endothelial dysfunction and increase in systemic capillary permeability. In kidney there is loss of barrier integrity and capillary leak in the glomerulus results in increased excretion of albumin in the urine. This study was done to evaluate the degree of microalbuminuria in sepsis in correlation with APACHE II score and to test whether the degree of microalbuminuria could predict the mortality in critically ill sepsis patients.

Methodology:

The present study was conducted on 50 patients admitted to Medical emergency/ Medical ICU in Madras Medical College and Rajiv Gandhi Government General Hospital,Chennai. Spot urine sample was collected within 6 hours and at 24 hours of admission to medical emergency/ICU ward. Sample tested for urine micro albumin by using immunoturbidometric method and for urine creatinine by jafee method. Urine albumin: creatinine ratio was calculated. (At 6 hours ACR-1 and at 24 hours ACR-2).APACHE II scoring was done at 24 hours of admission.

Patients was followed up during the course of hospital stay and the outcome of the patient (i.e. Death/Survival) is recorded.

Results:

The present study included 50 patients, among which 31 were males and 19 were females. Mean age was 43.5 years. Mortality was 38%. Mortality was more among male patients than in female. APACHE II score ranges from 6 - 37, mean APACHE II among survivors were 16.35 with Standard Deviation of 6.78 and among non survivors were 25.47 with Standard Deviation of 6.93 with p value of <0.0001 for predicting mortality.Urine ACR 1 was 74.06±20.83 µgm/mg among survivors and 164.53±46.61 µgm /mg among non survivors and ACR 2 was 45.81±17.92µgm/mg among survivors and 157.84±36.96 µgm/mg among non survivors. Both were statistically significant with p value of 0.0001 for predicting mortality. The degree of microalbuminuria correlates with disease severity.

Conclusion:

Significant microalbuminuria is predictive of mortality which is equivalent to APACHE II score. Microalbuminuria is an inexpensive and rapid diagnostic tool. Serial measurements may help in the clinical assessment of critically ill patients at risk of worse prognosis, even in resource poor areas.

KEYWORDS

Sepsis; microalbuminuria; APACHE II score; urine albumin creatinine ratio.

INTRODUCTION

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Sepsis is marked by a severe host defense response that involves triggering ofpotent inflammatory cascades which release a plethora of pro-inflammatory moleculesinto the circulation. The endothelium becomes dysfunctional due to the sustainedonslaught of the inflammatory molecules and the simultaneous oxidative stress. An earlyevent is the loss of barrier integrity leading to systemic capillary leak. Increased capillarypermeability is an early feature of Systemic Inflammatory Response Syndrome (SIRS).

The glomerular manifestation of this enhanced capillary permeability is increasedexcretion of albumin in the urine. In various studies microalbuminuria has beencorrelated with rapid changes in vascular integrity.Early prediction of mortality among critically ill sepsis patients and earlyinstitution of intensive therapy is of paramount importance which has significantimplications on survival of the patient.

Various ICU scoring systems to predict mortality are in current use like the APACHE II and SAPS II score. These scoring systems are cumbersome and are done at24 hours of admission during which precious time is lost in administering therapy.Microalbuminuria, defined as 30–300 mg/day of albumin excretion in the urine,occurs rapidly after an acute inflammatory insult such as sepsis and persists in patientswith complications. It is a common finding in critically ill patients, where it has shownpromise not only as a predictor of organ failure and vasopressor requirement but ofmortality. This study is an attempt to understand the usefulness of Urine Micro albumin andcreatinine ratio in predicting scoring the mortality of the patient and to compare it with validatedsystems such as APACHE II

Aims and Objectives of the study

1)To study the correlation between the degree of micro albuminuria and severity of sepsis.

2)To evaluate whether the degree of micro albuminuria could predict mortality in sepsis.

3)To develop a simple, inexpensive and dynamic marker of critical illness.

REVIEW OF LITERATURE

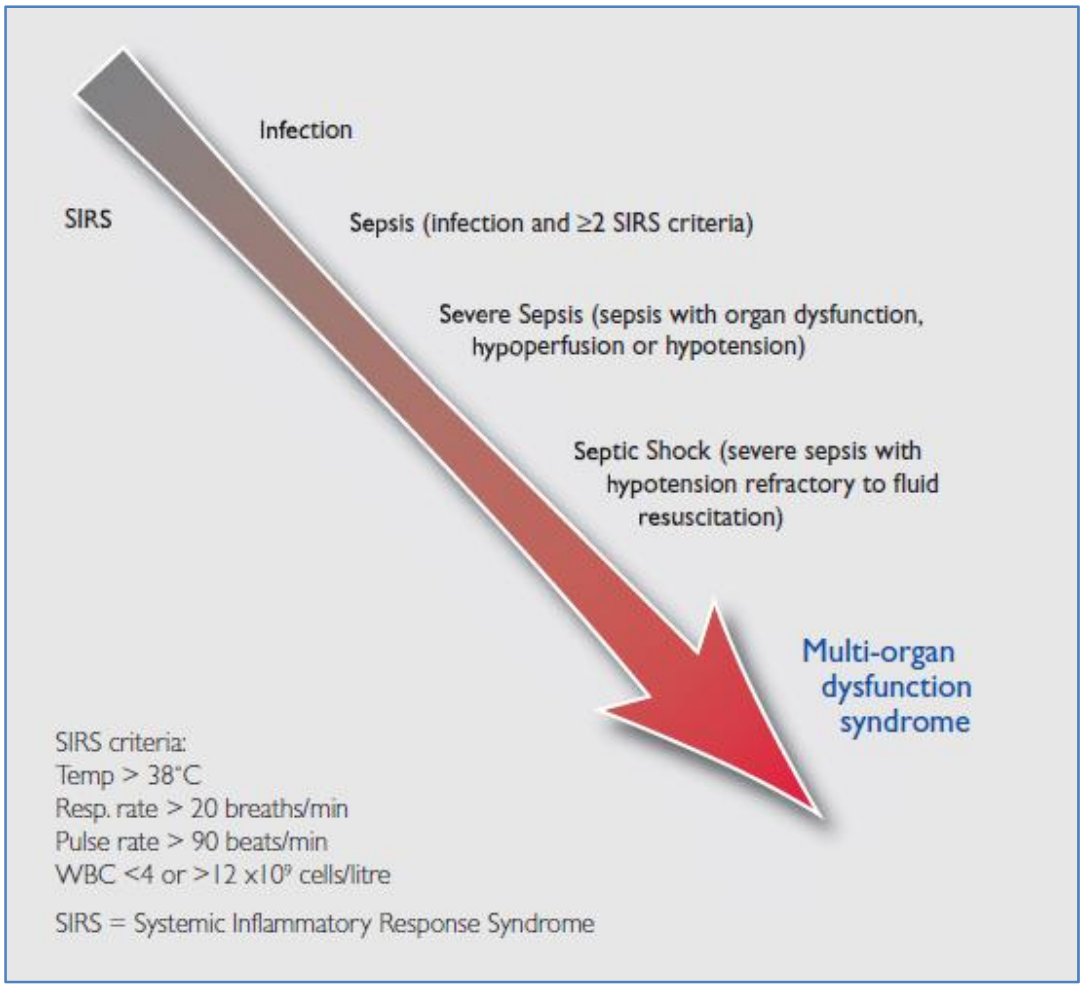
Definition

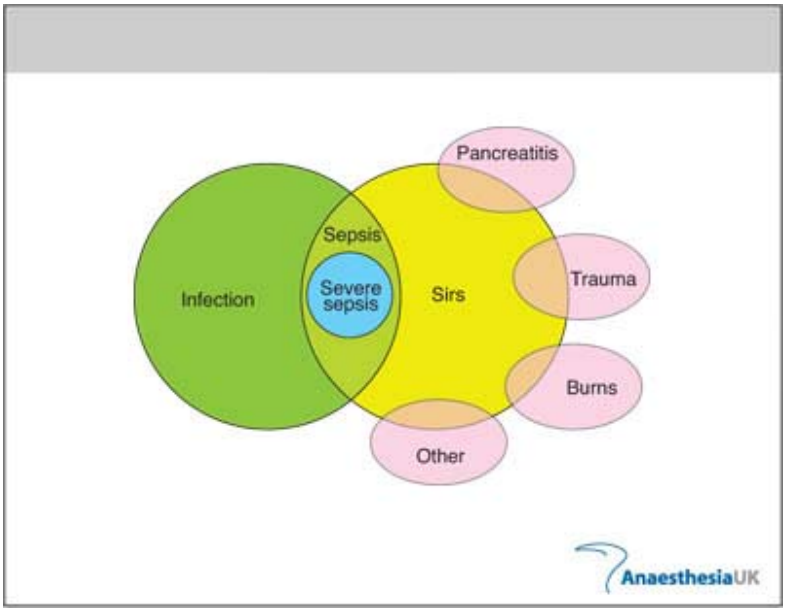
Septicaemias:

The term septicaemia implies active replication in the blood of bacteria associated with systemic manifestations. ‘Bacteraemia’ means the presence of bacteria in the blood which may be transient and without symptoms.

Septic shock :septic shock is characterized by hypotension (systolic BP less than 90 mmHg), hypoxia, increased serum lactic acid levels, high-anion-gap metabolic acidosis, and oliguria with a urine output of less than 30 ml/h. Multiple organ dysfunction which may also include disseminated intravascular coagulation leads to a mortality of up to 50 percent.

Sepsis has very high morbidity and mortality, which leads to major healthcare burden in the world. Though there is far advancement in the therapeutic options, the mortality rate remains high due to the delay in the diagnosis because of lack of availability of reliable diagnostic methods. There is significant improvement in the outcome of the patients in early goal directed therapy in severe sepsis and septic shock.


Infection
SIRS
Sepsis (infection and ≥2 SIRS criteria)
Severe Sepsis (sepsis with organ dysfunction, hypoperfusion or hypotension)
Septic Shock (severe sepsis with hypotension refractory to fluid resuscitation)
Multi-organ dysfunction syndrome
SIRS criteria:
Temp > 38°C
Resp. rate > 20 breaths/min
Pulse rate > 90 beats/min
WBC <4 or >12 x10⁹ cells/litre
SIRS = Systemic Inflammatory Response Syndrome


Pancreatitis
Sepsis
Infection
Severe sepsis
Sirs
Trauma
Burns
Other
AnaesthesiaUK

Bacteremia	Presence of bacteria in blood, as evidenced by positive blood cultures
Septicemia	Presence of microbes or their toxins in blood
Systemic inflammatory response syndrome (SIRS)	Two or more of the following conditions: **(1) fever** (oral temperature >38°C) or **hypothermia** (<36°C); **(2) tachypnea** (>24 breaths/min); **(3) tachycardia** (heart rate >90 beats/min); **(4) leukocytosis** (>12,000/μL), **leukopenia** (<4,000/μL), or >10% bands; may have a noninfectious etiology
Sepsis	SIRS that has a proven or suspected microbial etiology
Severe sepsis	Sepsis with one or more signs of organ dysfunction—for example: **1. Cardiovascular**: Arterial systolic blood pressure ≤90 mmHg or mean arterial pressure ≤70 mmHg that responds to administration of intravenous fluid **2. Renal**:Urine output <0.5 mL/kg/hr for 1 h despite adequate fluid resuscitation **3. Respiratory**: PaO2/FIO2 ≤250 or, if the lung is the only dysfunctional organ, ≤200 **4. Hematologic**: Platelet count <80,000/μL or 50% decrease in platelet count from highest value recorded over previous 3 days **5. Unexplained metabolic acidosis**: A pH ≤7.30 or a base deficit ≥5.0 mEq/L and a plasma lactate level >1.5 times upper limit of normal for reporting lab **6. Adequate fluid resuscitation**: Pulmonary artery wedge pressure ≥12 mmHg

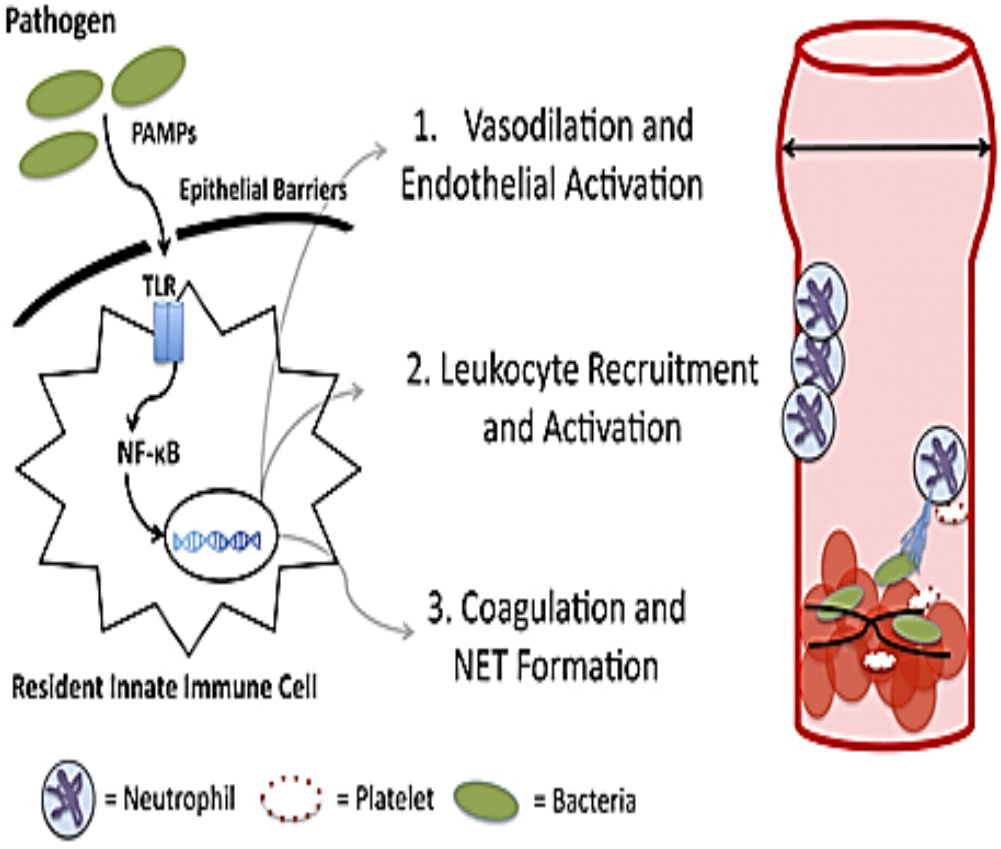
Septic shock	Sepsis with hypotension (arterial blood pressure <90 mmHg systolic, or 40 mmHg less than patient's normal blood pressure) for at least 1 h despite adequate fluid resuscitation; **or** Need for vasopressors to maintain systolic blood pressure ≥90 mmHg or mean arterial pressure ≥70 mmHg
Refractory septic shock	Septic shock that lasts for >1 h and does not respond to fluid or pressor administration
Multiple-organ dys- function syndrome (MODS)	Dysfunction of more than one organ, requiring intervention to maintain homeostasis
Predisposition-infection-response-organ dysfunction (PIRO)	A grading system that stratifies patients according to four key aspects of illness; attempts to define subgroups of patients, reducing heterogeneity in clinical trials
Critical illness related corticosteroid insufficiency (CIRCI)	Inadequate corticosteroid activity for the patient's severity of illness; should be suspected when hypotension is not relieved by fluid administration

Pathogenesis of sepsis syndrome

- Advances in unravelling the genetic basis and pathophysiology for the host responses to sepsis have changed the current understanding of the syndrome, and several therapies have shown surprising efficacy.In sepsis the antigens from infectious agent stimulate monocytes and macrophages which leads to release of pro inflammatory cytokines.
- This potent activation of inflammatory cascade leads to endothelial dysfunction and increase in systemic capillary permeability. The endothelial injury and capillary leak in the glomerulus results in increased excretion of albumin in the urine.

- In several systemic diseases renal involvement is the well-recognised complication. Renal blood flow contributes the major portion of cardiac output. Exogenous and endogenous agents involved in the pathogenesis of disease process traverse the glomerular circulation results in glomerular injury. This leads to the presence of microalbumin in the urine which is very well observed in multiple organ dysfunction syndrome (MODS).Albuminuria is the manifestation of glomerular capillary leak in diffuse systemic manifestation.

Early cellular and molecular events during infection.



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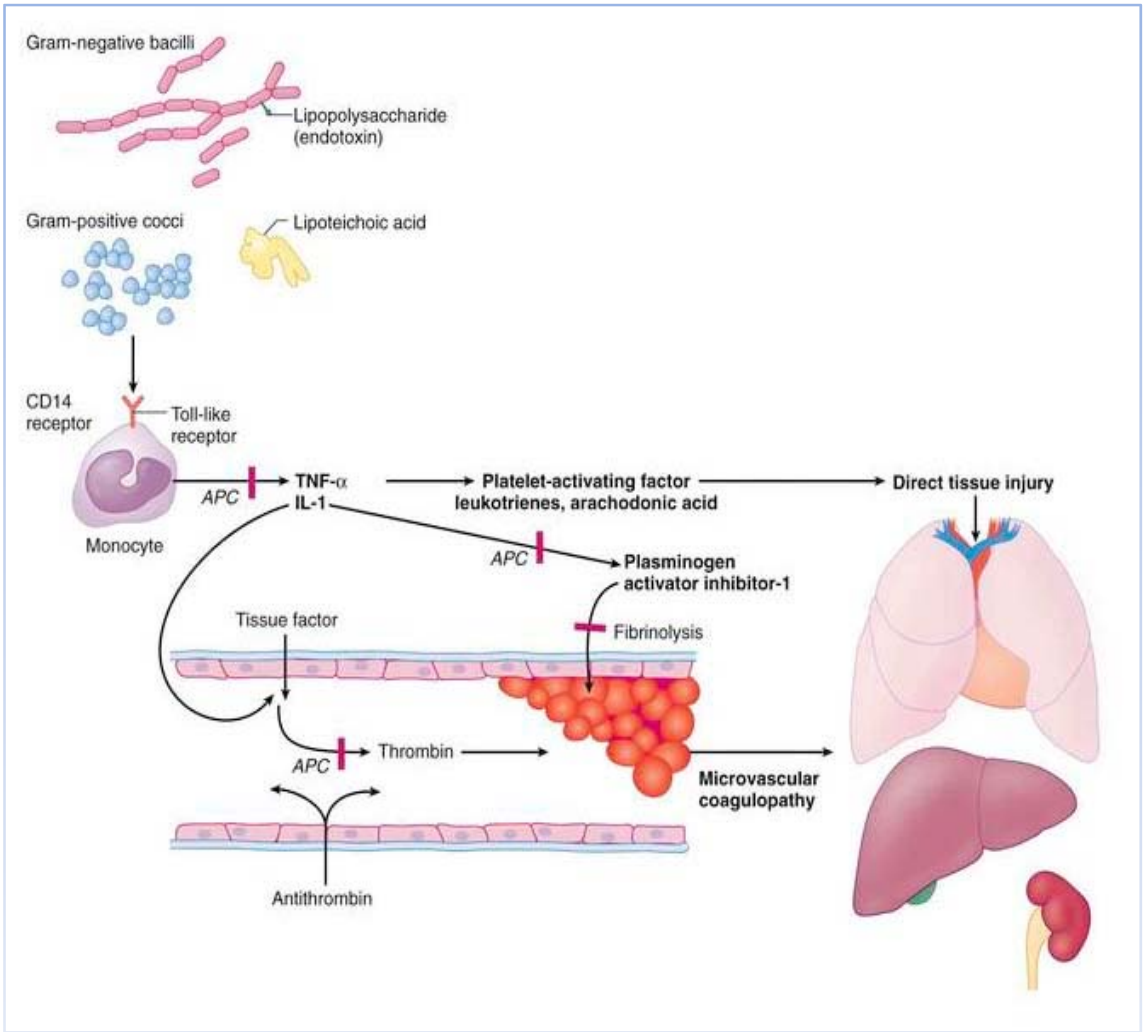


- **Microbial factors**

  Bacterial load

  Endotoxin (Gram -ve), teichoic acid (Gram +ve)

  Activation of complement cascade

- **Host factors**

  Systemic inflammatory response syndrome (SIRS)

  Release of immune mediators (IL-1 and TNF - a)

  Endothelial damage

  Activation of coagulation cascade

  Myocardial function

- **Result**

  Tissue perfusion , BP , sensorium

  Oliguria and azotaemia

  Adult respiratory distress syndrome (ARDS)

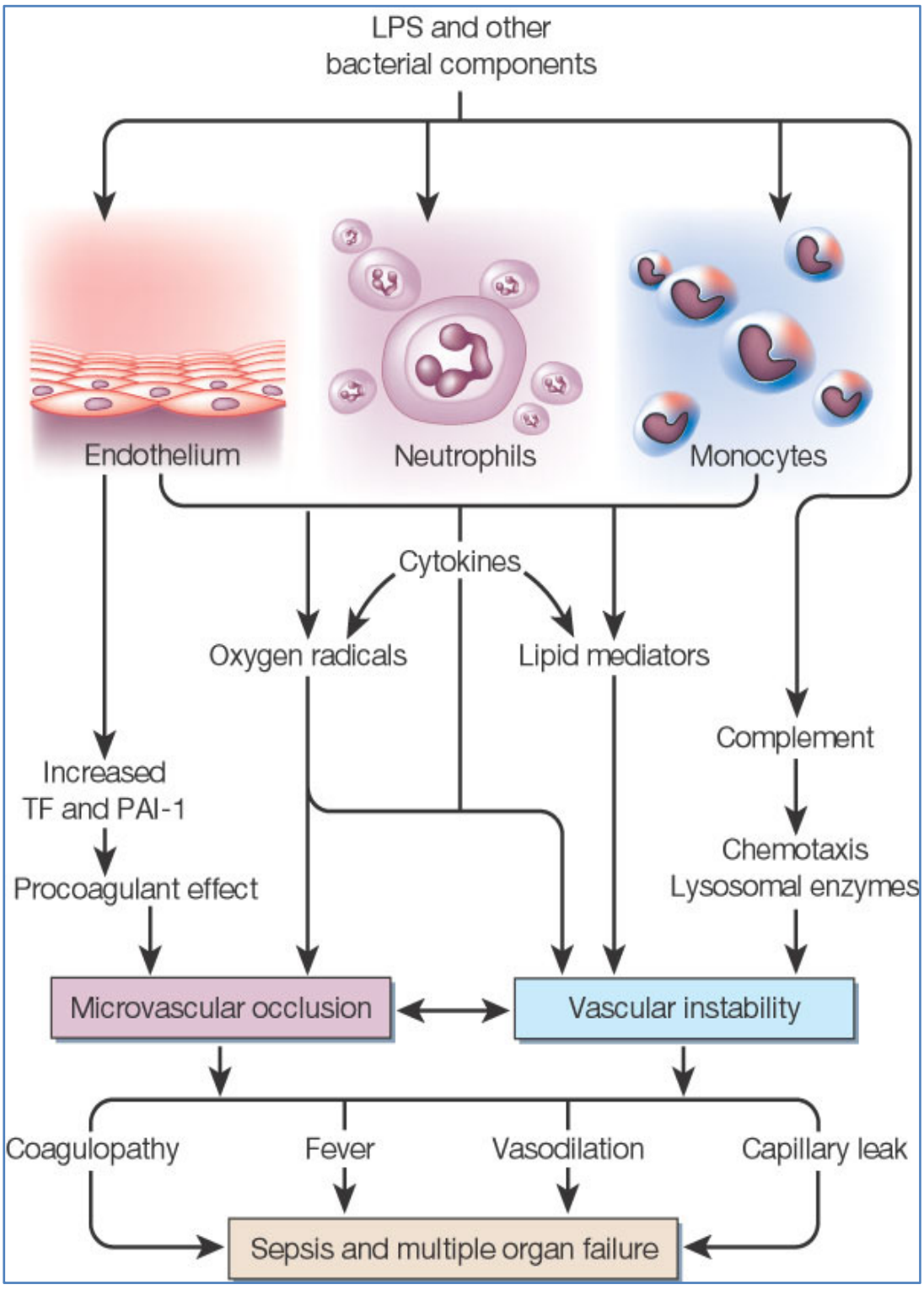
  Disseminated intravascular coagulation (DIC)

  Shock

T-cell receptor or immunoglobulins.

- The innate immune system is activated by cell wall components and secreted proteins which are produced by the microorganisms . Gram negative cell walls contain bacterial endotoxin and lipopolysaccharide .Both

of them are important in the pathogenesis of sepsis.[1,2,3].



- There are two components in endotoxin . Lipid A is a component of endotoxin which plays a major role in immunostimulation.[3]The humans are more susceptible to the immunostimulation of sepsis.

Lipopolysacharide

- LPB is the binding protein for lipopolysaccharide. After binding to LPB , it is transferred to CD 14 expressed by leukocytes.[4,5] Bactericidal increasing protein is produced by polymorphonuclear cells and it causes modulation of the activity of LPS prevents LPS from binding to LPB. Binding of LPS to LPB results in induction of signal transduction, resulting in toll-like receptors (TLRs)activation .[6,7] Which is mediated by CD14.

Toll like receptors

- TLRs are present even in invertebrates and plants. It causes regulation of defense against the microorganisms. Ten TLRs have been discovered .
- The ligand specificity of TLR is of wide range like lipoproteins,peptidoglycan, lipopolysaccharide, and lipoteichoic acid from various pathogens .[8] TLR4 is the lipopolysaccharide receptor, Gram + cell wall components are predominantly recognized by TLR2, while flagellin is recognized by TLR5 and bacterial DNA is recognized by TLR9. The TLRs

are transmembrane proteins. Toll like receptors and interleukin (IL)-1 receptor have similar cytoplasmic domain .[9]

- The role of toll like receptors are studies in the mice having mutations in the gene of toll like reptors.[11,12]Mice with mutations in toll like receptor 4 gene did not have any response to lipopolysaccharide and were resistant to toxic shock but mice with mutations in toll like receptor 2 gene were susceptible.[13]
- Sepsis itself has been demonstrated to up-regulate expression of TLR2 and TLR4 .[14]In experimental models, immunomodulators that decrease expression or activation of TLRs decrease lethality. It has therefore been proposed that the exaggerated proinflammatory response characteristic of the acute respiratory distress syndrome (ARDS), SIRS, and severe sepsis may be due to overexpression of TLRs or the consequent excess activation of NF-kappaB and other nuclear transcription factors.[15]
- Other than TLRs several other pathway by which recognition of microorganism is possible by the cells have been discovered . They are

1.Peptidoglycan-recognition proteins (PGRPs).[16,17] Different PGRPs can distinguish between Gram-positive and Gram-negative bacteria.

2.TREM-1 and MDL-1 cause activation of monocytes .[18,19]

- There is a severe activation of innate immune system following initial interaction with microorganism which causes coordination of cellular and humoral components of immunity. Monocytes and lymphocytes release proinflammatory molecules Interleukin-1, Interleukin-6, and tumor necrosis factor-alpha, but in addition to it Interleukin-8, Interleukin-12, Interleukin-15,and Interleukin-18.
- In addition antiinflammatory mediators (IL-4, IL-10, IL-ra) are produced to balance the proinflammatory mediators in an attemptto eliminate the foreign antigen. Pro inflammatory and antiinflammatory pathways are tightly regulated. These pathways are closely connected to other pathways involved in homeostasis.

  To name a few,

- Lipid mediators
- Neutrophil-endothelial cell activation
- Coagulation/fibrinolytic system
- Nitric oxide production
- Oxidant/antioxidant pathway
- Acute phase proteins
- Hypothalamic-pituitary-adrenal axis
- Cell apoptosis

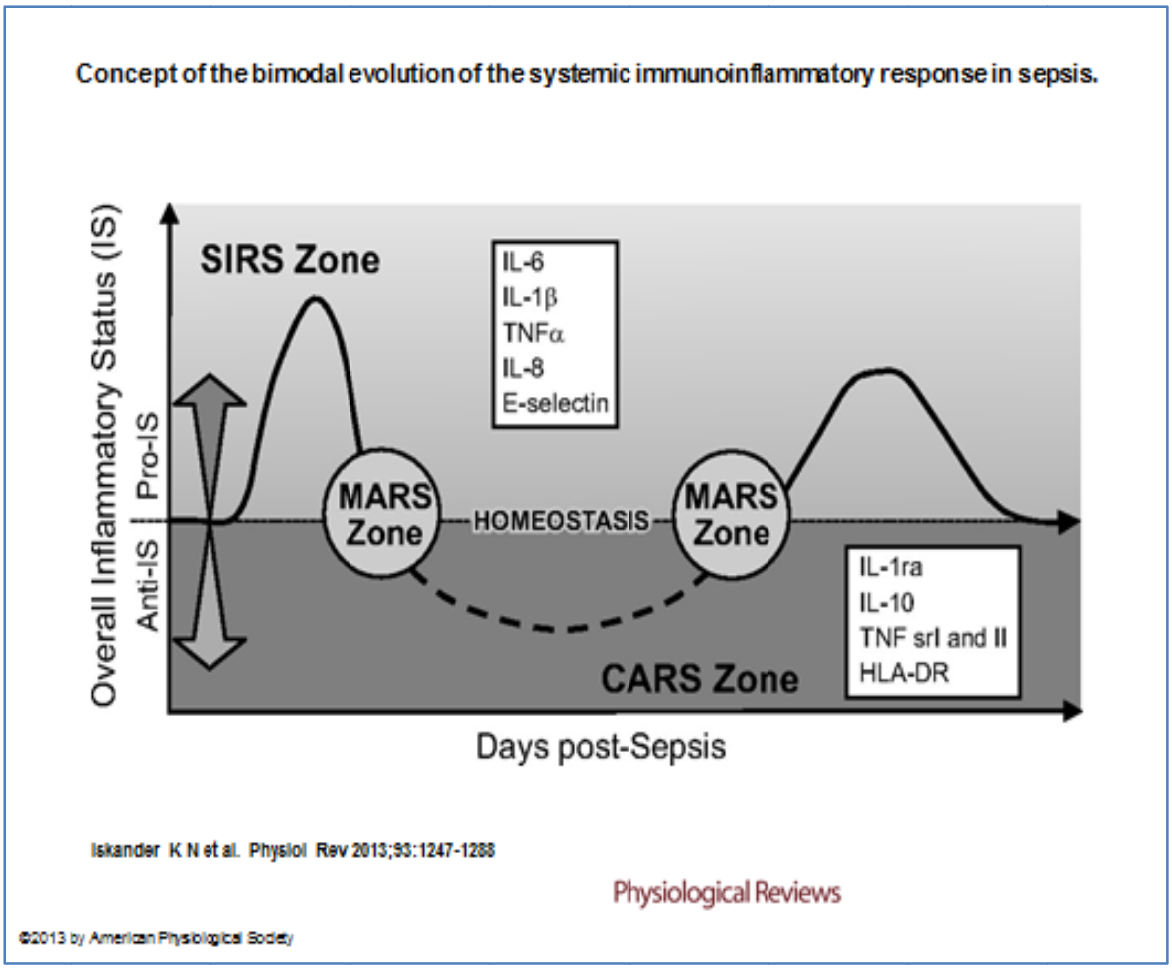
- Heat-shock proteins
- All these pathways are liked with the feedback loops in a very complexed manner. Severe sepsis and septic shock occurs due to dyregulated homeostatic mechanisms.
- TNF-alpha is the first proinflammatory cytokine to be released in sepsis, followed by interleukin-1, interleukin-6, and interleukin-8.[20,21] Tumor necrosis factor and interleukin-1 aresynergistic as well as similar in action.[22-26] Second messengers are generated after they bind to the receptors . the second messengers are phospholipase A2 and C , G proteins, oxygen free radicals and adenylcyclase.
- In addition, a number molecule production are induced such as,
    1. ELAM
    2. Tissue factor
    3. ICAM-1
    4. Cyclooxygenase
    5. Fibrinolytic proteins
    6. Plasminogen activator inhibitor-1
    7. Clotting proteins
    8. Plasminogen activator
    9. Phospholipase A2 (PLA2)

10.Nitric oxide synthetase

- The antiinflammatory cytokinesare interleukin-4, interleukin-10, interleukin-13, and transforming growth factor-beta2. Switching of TH1 to TH2 activation is done by anti inflammatory cytokines. Interleukin-1 and TNF-alpha are suppressed by them.

ANNEXIN -1

- Annexin-1 (ANXA-1), previously named lipocortin-1, is a 37kd protein produced by mononuclear cells during the resolution phase of sepsis that has potent antiinflammatory properties and protects against LPS lethality.[27,28]
- ANXA-1 inhibits PLA2, inducible nitric oxide synthetase (iNOS), and cyclooxygenase-2 (COX-2), while it increases interleukin-10 release by macrophages.[29] ANXA-1 prevents neutrophil adhesion to activated endothelium and inhibits neutrophil migration.[30,31]
- The antiinflammatory cytokines is to keeps the inflammation under control. Homeostasis is achieved by a balanced pro and antiinflammatory mediators. SIRS and MODS occurs when this homeostasis is affected.[32]Excessive anti-inflammatory cytokines will cause anergy resulting in a state more prone for infection.[33]



Coagulation System Activation

- Procoagulant pathway is activated in sepsis due to inbalance in hemostasis.[34]This imbalance is the main cause of organ dysfunction in sepsis. Coagulopathy occurs because of activation of coagulation pathway.[35] This results in disseminated intravascular coagulation, which is characterized by intravascular thrombosis. It is strongly implicated in the pathogenesis of organ failure in sepsis .

TISSUE FACTOR

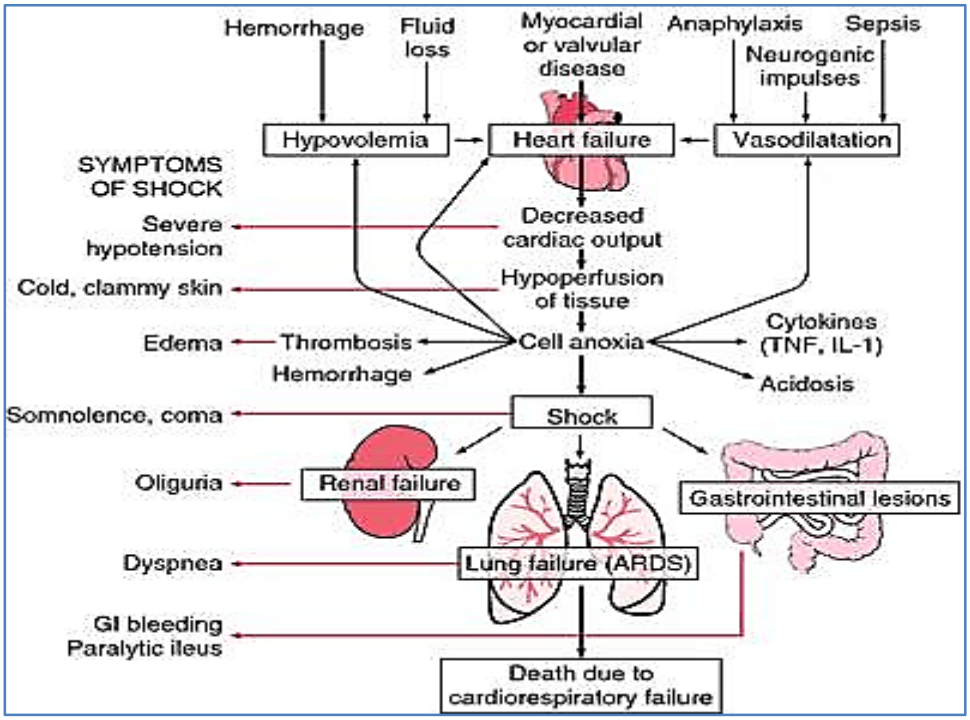
- The extrinsic pathway of coagulation system is mainly involved in the pathogenesis of sepsis. Intrinsic pathway can also be activated in sepsis by the endotoxin .Tissue factor is highly thrombogenic.
- Tumor necrosis factor-alpha, interleukin 1, and plasminogen activating factor complement increased tissue factor expression. The main source of tissue factor in sepsis is the granulocytes and monocytes.
- Antibodies against tissue factor has been studied in experiment models. They have demonstrated the suppression of coagulation cascade .Tissue factor pathway inhibitor (TFPI) ,Thrombomodulin pathway and ATIII suppress the tissue factor mechanism

The Microcirculation in Sepsis

- Using orthogonal polarization spectral imaging, De Backer et al.[36,37]have demonstrated that as compared to control, patients with sepsis have a marked reduction in the number of small capillaries that are perfused, and that the microvascular flow improves with time in survivors but not in nonsurvivors.

- Furthermore, these authors and others have demonstrated that the microcirculatory changes with sepsis are rapidly reversed with vasodilators (topical acetylcholine, dobutamine, and intravenous nitroglycerine).[38,39]
- The role of vasodilator agents such as nitroglycerine and prostacyclin, which recruit capillaries and improve microcapillary flow in the management of sepsis, requires further study.[40-42]
- In a LPS model, Iba et al. demonstrated that recombinant human activated protein C (rhAPC) improved microcirculatory flow through the inhibition of leukocyte-endothelial interaction and suppression of proinflammatory cytokine production .[43]

ORGAN INVOLVEMENT IN SEPSIS



Glucocorticoid in sepsis

- Whether critically ill patients commonly have adrenal failure is difficult to dispute.[44,45] What remains controversial at this time is the diagnosis of this disorder. Although a random total serum cortisol or a total cortisol following 250 µg corticotropin is commonly used to diagnose adrenal insufficiency, this test has a number of limitations.
- Cortisol binding globulin decreases during infection and the affinity of the hormone to bind is also decreased during acute illness ,resulting in an increase in the free biologically active fraction of the hormone.
- Furthermore, due to alterations in GR number and/or function neither the total nor free cortisol reflects tissue glucocorticoid activity.
- Nevertheless, despite these limitations, a random total cortisol of less than 15 µg per dL or a level less than 20 µg per dL after 250µg corticotropin in a patient with severe sepsis is generally regarded as diagnostic of CIRCI .

Diagnosis

Laboratory studies that may be considered include the following:

- Complete blood count (CBC) – Usually not helpful

- Platelets are elevated in inflammation reduced in DIC
- WBCs are usually elevated but sometimes suppressed
- Coagulation studies Elevated prothrombin time, APTT
- D-dimer in DIC, decreased fibrinogen levels in DIC
- Renal function tests Abnormal in hypoperfusion renal failure
- Liver function tests Helpful in localizing sepsis; consider biliary sepsis, especially in elderly patients with no obvious localizing signs
- Blood cultures :Three sets of cultures must be obtained in all patients before administration of antibiotics
- Urine cultures Part of the diagnostic workup for sepsis
- Bacterial cultures – Blood cultures at admission; culture of the catheter tip (for suspected central IV line sepsis); nasal cultures (potential marker of MRSA risk)
- Stained buffy coat smears or Gram staining of peripheral blood
- Urine studies (Gram stain, urinalysis, and urine culture)

- Procalcitonin levels

Imaging modalities that may be helpful include the following:

- Chest radiography (to rule out pneumonia and diagnose other causes of pulmonary infiltrates)
- Abdominal ultrasonography (for suspected biliary tract obstruction)
- Abdominal CT or MRI

The following cardiac studies may be useful if acute myocardial infarction (MI) is likely:

- Electrocardiography (ECG)
- Cardiac enzyme levels

Invasive diagnostic procedures that may be considered include the following:

- Thoracentesis (in patients with substantial pleural effusion)
- Paracentesis (in patients with gross ascites)
- Swan-Ganz catheterization (for helping manage fluid status and assessing left ventricular dysfunction in MI; not for diagnosis of sepsis per se)

- Lumbar puncture

- cerebrospinal fluid examination :Performed after cerebral computed tomography in suspected meningitis; antibiotics should not be withheld until after cerebrospinal fluid is obtained

MORTALITY AMONG PATIENTS WITH SEPSIS

Severity of Disease Mortality (%)

Systemic inflammatory response syndrome	: 7 %
Sepsis	:16%
Severe sepsis	:20%
Septic shock	:46%

UNFAVOURABLE FACTORS IN SEPSIS

Host Factors

- Hypothermia (temperature < 35.5°C)
- Leukopenia (WBC < 4000/mm3)
- Arterial blood pH < 7.33
- Shock
- Multiorgan dysfunction (renal failure, respiratory failure, cardiac failure)
- Age > 40 years

Medical comorbidities

Controversial Risk Factors

Serum cortisol level

Factors Under Study Risk

Genetic polymorphisms (in genes encoding TNF-α, IL-1, IL-6)

MANAGEMENT OF SEPSIS

MANAGEMENT PRINCIPLES

TREATMENT

1) Identification and elimination of the septic foci

- Removal of infected catheters or venous access devices
- Identification and drainage of abscess
- Debridement of infected tissue

2) Fluid resuscitation guided by vital signs (including central venous pressure) and urine output.

3) Initiate vasoactive agents if needed.

4) Place central venous catheter and arterial cannula if needed.

5) Obtain antimicrobial cultures

6) Broad-spectrum antibiotics (based on the particular risk factors for infection) and assessment of the patient's immune state.

7) Supportive care and management of other symptoms

- Oxygen, to keep saturations greater than 90 mm Hg
- Treatment of delirium ,nausea ,vomiting and pain .
- Intravenous Insulin for hyperglycaemia
- Activated protein C (drotrecogin alfa)
- Initiate prophylactic measures for venous thromboembolism and gastrointestinal haemorrhage
- Initiate lung protective ventilation strategies

ANTIBIOTIC THERAPY

- The important management is to identify the organism, eradicate the focus of infection, eliminate pathogens from the blood stream, and correct organ dysfunction. Prompt and aggressive treatment is often successful but once septic shock supervenes the mortality rises sharply.

- Organisms causing sepsis in the community differ from those causing sepsis in hospital (nosocomial infection)
- Fungal infections are seen today in increasing numbers in patients who are immunosuppressed because of renal transplants, malignancy or AIDS. Neutropenic patients are a special group where infections with Pseudomonas aeruginosa, Staphylococcus epidermidis and fungi (candida, aspergillus) are common.
- Community-acquired sepsis with skin rash constitutes a distinct group where one has to consider conditions like toxic shock syndrome (Staph. aureus) or meningococcal septicaemia.The choice of antibiotics depends on the organism suspected and on the results of cultures.
- Intravenously administered bactericidal antibiotics are required, occasionally in synergistic combination. Drug pharmacokinetics are altered in critically ill patients, requiring diligent attention to dosage schedules

	Infections	**Organisms**	**Antibiotics**
1.	Community-acquired urinary tract infections	E. coli Klebsiella	Sulphatrimethoprim Ampicillin Quinolones Aminoglycosides

2.	Community-acquired respiratory infection	S.pneumoniae H.influenza Legionella	Ampicillin with clavulanic acid Erythromycin Sulphatrimethoprim
3.	Community-acquired infection with skin rash	Staph.aureus Meningococcus	Cloxacillin Ampicillin with clavulanic acid Chloramphenicol Ceftriaxone
4.	Nosocomial sepsis	Pseudomonas aeruginosa Enterobacter Serratia E.coli Acinetobacter	Ceftazidine Cefaperazone Aminoglycosides Imipenem Aztreonam Antipseudomonal penicillins
5.	Sepsis with neutropenia	Pseudomonas aeruginosa Staphylococcus Fungi	As above Vancomycin Amphotericin

Hemodynamic Support :

Intravascular Volume Expansion

COLLOIDS

- Because of increase in capillary permeability the interstitial volume is increased . Interstitial fluid volume will be increased by crystalloid solutions so they should be avoided for resuscitation. Colloidal solutions have more advantage over crystalloids. [46-48]
- Albumin and hydroxyethyl starch (HES) solutions are the colloidal solutions most commonly used in patients with sepsis. HES has a number of theoretical advantages over albumin. These solutions remain largely intravascular, with maintenance of an osmotic gradient for up to 200 hours post infusion .[49]In comparison, in septic patients albumin redistributes into the interstitium, expanding the interstitial volume equal to the volume of infused albumin.
- In addition, HES solutions have antiinflammatory properties and inhibit endothelial activation and endothelial-associated coagulation, resulting in less tissue edema.[50-56].
- The use of albumin in critically ill patients has been controversial. A well-publicized metaanalysis of the use of albumin in critically ill patients

published in the British Medical Journal suggested that albumin administration increased mortality .[57]

- In a recent landmark study, the Australian and New Zealand Clinical Trials Group (ANZICS) compared the effect of fluid resuscitation with 4% albumin with that of saline on mortality in 6,997 heterogeneous ICU patients.[58]
- This study provides evidence that albumin is not harmful in critically ill patients with a suggestion that this volume expander may be preferable to saline in patients with sepsis.
- In the absence of strong evidence, it is recommended that a resuscitation algorithm that combines the use of a crystalloid and colloid HES. Limiting the volume of crystalloids in this manner may decrease tissue edema, improve tissue oxygenation, and reduce complications. Such an approach has been demonstrated to reduce complications in postoperative patients .[59]

Vasoactive Agents

- Vasopressor therapy should be started if the patient fails the fluid challenge. In case of life threatening situations vasopressor therapy is immediately started.

- In spite of fluid resuscitation patients remain hypotensive because of peripheral vasodilation. Septic patients are hypo responsive to vasopressors hence high dose is needed.
- Multi organ failure occurs because of failure to increase the tissueperfusion. However the right choice of inotropic agents in patients with sepsis are yet to be determined .

NOREPINEPHRINE

- Norepinephrineis the first-choice vasopressor agent in sepsis.[60] Norepinephrine increases MAP due to its vasoconstriction, with little On comparing with dopamine heart rate and stroke volume are less affected.
- Norepinephrine increases tissue oxygenation and splanchnic perfusion.Dopamine was initially the vasopressor of choice in sepsis .the chronotropic effect is not desired . Tachycardia and tachyarrhythmias are the major disadvantages.

DOPAMINE

- Myocardial oxygen consumption is increased in dopamine therapy resulting in myocardial ischaemia.
- GI mucosal ischaemia is caused by dopamine.

- Prolactin is needed in patients with sepsis which is decreased in patients with sepsis.
- Patients who remain hypotensive, have poor urine output after adequate volume resuscitation (4 to 5 L of crystalloid or equivalent) and are receiving high doses of norepinephrine (greater than 0.3 to 0.5 μg per kg per minute) require noninvasive or invasive hemodynamic monitoring.
- Hypotension/inadequate organ perfusion in this situation may be due to severe vasodilatation, inadequate volume resuscitation, and/or severe ventricular dysfunction; the distinction between these entities is difficult to make clinically, and, therefore, hemodynamic monitoring is required.
- Most patients with sepsis have a hyperdynamic circulation with a high cardiac output. However, some patients with septic shock have severely depressed myocardial function. This may arise either due to preexistent heart disease or sepsis-induced ventricular dysfunction. In this situation ventricular function and cardiac output are best assessed by bedside transthoracic echocardiography or pulmonary artery catheterization.

VASSOPRESSIN

- Patients with poor left ventricular contractility despite adequate fluid resuscitation should receive a trial of dobutamine. Low-dose vasopressin

(0.01 to 0.04 U per minute) may be considered .While increasing blood pressure, experimental and clinical studies have shown that vasopressin (without a catecholamine) decreases oxygen consumption.

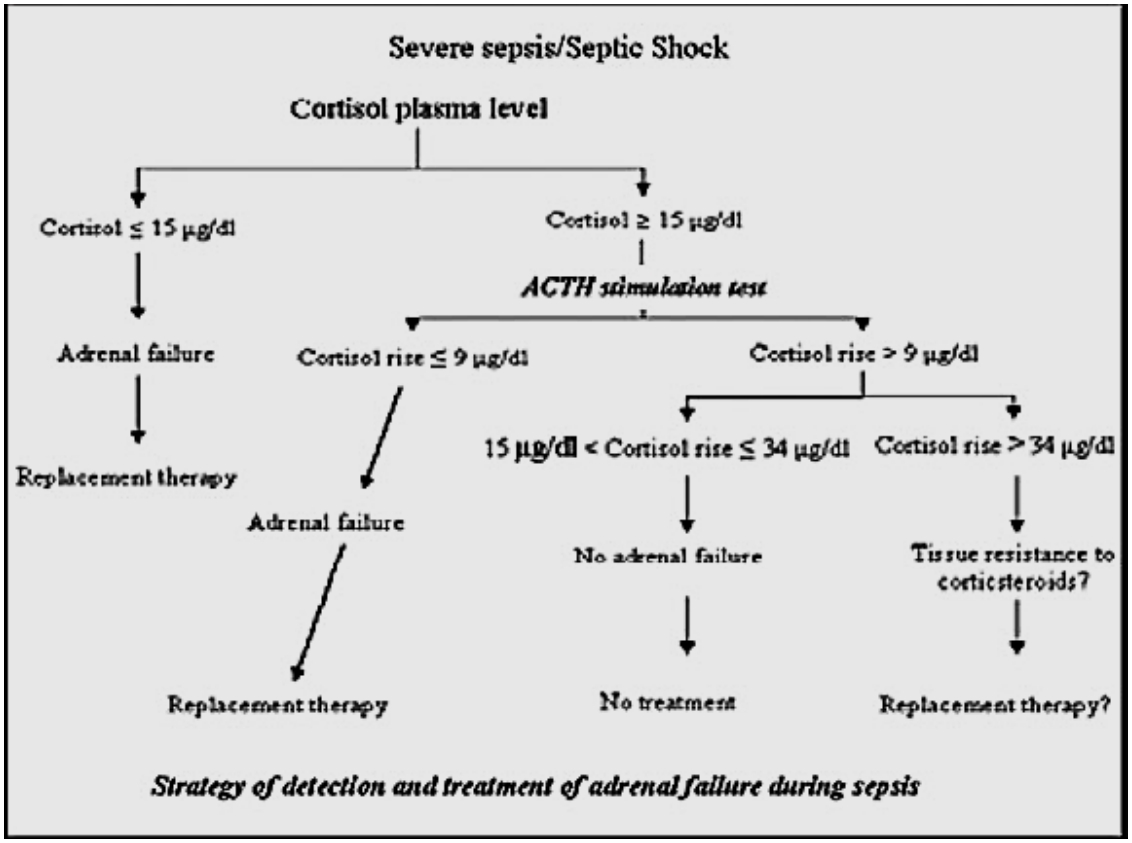
- In addition, in both clinical and experimental studies vasopressin has been demonstrated to cause vasoconstriction of the mesenteric artery and to compromise gut mucosal microcirculation. vasopressin should only be used in patients with refractory septic shock (norepinephrine greater than 0.5 to 1.0 μg per kg per minute) .
- Due to its effects on cardiac output and oxygen flux, vasopressin should be used in conjunction with a catecholamine (norepinephrine) .

EPINEPHRINE

- Serum lactate level is increased in patients treated with epinephrine. This increase in serum lactate level does not occur with other vassopressors.The increased lactate production may be due to increased glycogenolysis or a maldistribution of blood flow. In addition, in a canine septic shock model, compared with concurrent controls, which received antibiotics and intravenous fluid, the addition of epinephrine adversely effected survival .
- There are limited data on phenylephrine in sepsis. Phenylephrine lowers the cardiac output .

- Outcome improves if early dialysis is stared in patients who don't improve with aggressive fluid management .Continuous Renal replacement therapy is preferred as it does not cause much of hemodynamic unstability.

Treatment with Stress Doses of Hydrocortisone



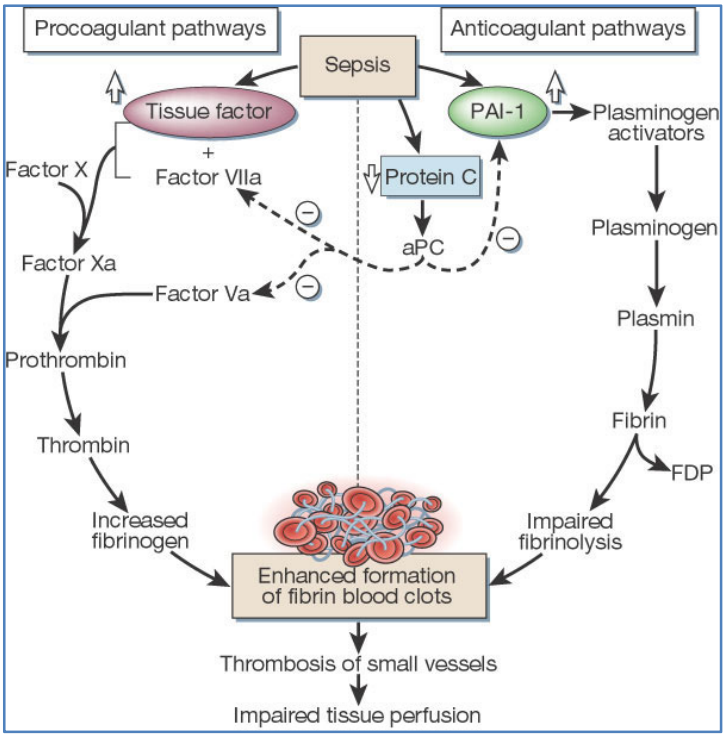
- In patients with vasopressor-dependent septic shock there has been a great deal of interest regarding the assessment of adrenal function and the indications for steroid replacement therapy. Treatment of septic shock with

stress doses of hydrocortisone has been demonstrated to improve the hemodynamic status, down-regulate the proinflammatory response, and improve mortality .

- Annane et al. in a landmark study, randomized 299 patients with septic shock to receive either hydrocortisone (50 mg intravenous every 6 hours) or placebo for 7 days.[61] Patients were stratified as responders (delta cortisol greater than 9 mg per dL) or nonresponders (delta cortisol less than 9 mg per dL) based on a 250-μg corticotrophin test.
- In this study 77% of patients were nonresponders. Overall the 28-day mortality was 55% in the steroid-treated group and 61% in the placebo group; in the nonresponders who were treated with hydrocortisone the mortality was 53%, and this compared to 63% in the nonresponders treated with placebo.
- By Kaplan-Meier analysis the 28-day probability of survival was significantly better in the steroid treated group compared to the placebo group (odds ratio of 0.71; 95% CI, 0.53 to 0.97; p = 0.03).
- Based on these data, treatment with hydrocortisone should be considered in all patients with septic shock. The role of adrenal function testing and treatment with stress doses of hydrocortisone in other groups of critically ill ICU patients remains to be determined.

Anticoagulation in Sepsis

- Coagulation cascade activation results in extensive thrombosis which results in the development of multi organ dysfunction syndrome. As the alteration in microcirculatory blood flow is postulated to play a major role in thepathophysiology of sepsis



- Studies have tested antithrombotic drugs in sepsis treatment. There is no evidence that mortality in sepsis decreases with heparin.

- Blood coagulation and inflammation can be suppressed by anti-thrombin III. Minimal levels of anti-thrombin III is present in sepsis .there may be a role of anti-thrombin III in treatment of sepsis.
- Protein C levels are decreasedin patients with sepsis .Protein C levels are low in survivors than non survivors . Bernard et al. , in a randomized multicenter, double-blind trial (PROWESS) studied the efficacy of drotrecogin alpha activated (APC) on 28-day all-cause mortality rate in patients with severe sepsis. [62]
- Patients were randomly assigned to receive a continuous infusion of APC at 24 μg per kg per hour or placebo intravenously for 96 hours. Subjects were randomized within 24 hours of onset of sepsis-related organ failure, such that the maximum time window for receipt of the study drug was 48 hours. A total of 1,690 randomized patients were treated (840 in the placebo group and 850 in the APC group).
- The mortality rate was 30.8% in the placebo group and 24.7% in the APC group. APC was associated with a 19.4% (95% CI, 6.6 to 30.5) relative risk reduction and 6.1% absolute reduction in the risk of death (P = 0.005). A post hoc analysis revealed that the benefit was observed among subjects who had APACHE II scores of 25 or more (a 13% absolute reduction), while the subjects with lower risk showed no benefit from APC. Other subgroups in

which APC was beneficial included patients older than 50 years of age, patients with more than one organ system dysfunction, and patients who had shock at the time of the infusion .

- In addition to inhibiting thrombosis and promoting fibrinolysis, APC inhibits leucocyte-endothelial interactions and suppresses inflammatory cytokine production, thereby attenuating the microcirculatory injury of sepsis . These properties of protein C may partly explain why APC appears beneficial in sepsis, yet other anticoagulants such as ATIII have failed to improve the outcome in patients with sepsis.

Summary of Advances in Managing Sepsis Based on Randomized Controlled Clinical Trials

- Recombinant human activated protein C improves survival for severe sepsis.[62]
- Hydrocortisone in septic shock improves immunologic and hemodynamic effects, but not outcomes .
- Early goal-directed therapy improves outcomes in sepsis and septic shock.
- No difference in outcomes with routine changes or exchanges or no change of long-term catheters.

- Most important treatment of nonneutropenic Gram-negative bacteremia is appropriate antibiotics, not combination therapy.

- 0.9% NaCl, 5% albumin (0.9% NaCl), Hespan (and not Hextend), and especially hypertonic saline solutions contribute to hyperchloremic metabolic acidosis and may decrease renal and splanchnic blood flow.

  Tifacogin (recombiant tissue factor pathway inhibitor) in severe sepsis has no effect on all cause mortality in those with increased international normalized ratio. It does increase the risk of bleeding irrespective of international normalized ratio .[63]

- In OPTIMIST study treatment with tifacogin did not decrease the mortality in the patients with severe sepsis.[63]

Blood component therapy

- Blood component therapy is dangerous in sepsisbecause the infused fibrinogen serves as a substrate which will further worsen the hemostasis. Coagulation factors infused will be destroyed by the circulating plasmin.
- Administration of FFP increased the mortality in meningococcal sepsis in a study of 336 patients.[64]
- Patients having hemorrhage severe thrombocytopenia and abnormal coagulation profile should be treated with fresh frozen plasma and platelets.

Should probably be coadministered with APC. Fibrinogen concentrates are not to be used. Coagulation profile should be closely monitored in replacement therapy.

MODS

Definitions

- Bone and others originally classified many of these patients with severe acute illnesses as having sepsis or the sepsis syndrome.[65,66] Efforts by these investigators to develop a consensus led to the terms SIRS and MODS.
- MODS has been defined as the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.
- Multi organ dysfunctionsyndrome is not an all-or-none condition, but rather a continuum. This important concept is incorporated in new definition of sepsis. Additional definitions commonly used in conjunction with MODS include SIRS, the compensatory antiinflammatory response syndrome (CARS), and the mixed antagonists response syndrome (MARS) .

Epidemiology

The frequency of multi organ dysfunction syndromeranges from 7% in patients suffering from multiple trauma, to 11% in the Intensive care unit patients. More than 60 % of deaths in surgical ICU is due to multi organ dysfunction.

Etiology

- In a survey of 2,475 patients with MODS, Zimmerman et al. found that nonoperative diagnoses accounted for most (76%) patients with MODS in the ICU.[67] These authors found that six primary reasons for ICU admission accounted for half of the nonoperative diagnoses including sepsis, pneumonia, congestive heart failure, cardiac arrest, and upper gastrointestinal bleeding.
- Most of the patients with MODS have been diagnosed to have sepsis. Patients may develop multi organ dysfunction syndrome as a consequence of a primary infection orfollowing nosocomial infections .
- In more 30 % patientswith MODS, no focus of infection can be found on clinical examination or postmortem studies.
- Other risk factors for the development of MODS include severity of disease (Acute Physiology and Chronic Health Evaluation [APACHE] II and III scores, resuscitation from circulatory shock, focus of devitalized tissue,

preexisting end-stage liver failure, age greater than 65 years, major operations, andsevere trauma.[68,69]

Mechanisms of Multiorgan Dysfunction Syndrome

The progression of organ dysfunction occurs in predictable manner. Respiratory failure is the first one to occur . It occurs in 72 hours.

Liver failure :5 to 7 days)

G I bleeding :10 to 15 days)

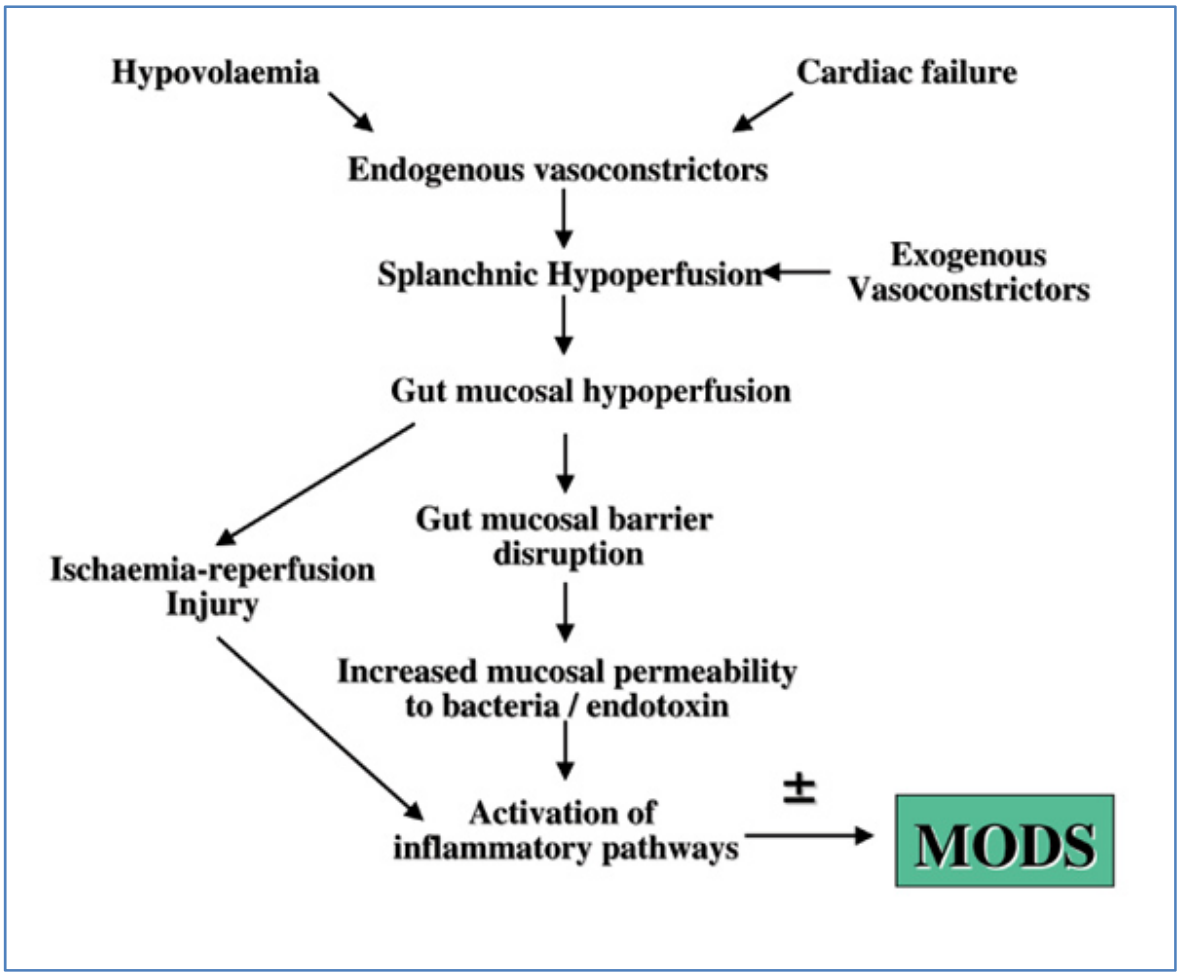
Kidney failure :11 to 17 days)

The pathophysiology of multi organ dysfunction syndrome is not well known.

Few postulated hypotheses are,

Gut Hypothesis:

- It is the most widely accepted theory. Splanchnic hypoperfusion can commonly occur following trauma, sepsis, shock.



- The diameter of central arteriole of villus is decreased by endotoxin which is dose dependent.
- The gut requires more oxygen , hence they are more susceptible to hypoxia resulting in mucosal ischaemia.
- The gut is highly susceptible to diminished tissue perfusion and oxygenation as it has a higher critical oxygen requirement than the whole body and other vital organs, and the mucosal counter-current microcirculation renders the

villi particularly vulnerable to ischemia . Mucosal ischemia leads to both structural changes and alterations in cellular function.

- Reactive oxygen species are produced resulting in impairment of mitochondrial respiration .
- Liver dysfunction may result in entry of the endotoxin into the circulation resulting in other organ injury.

Endotoxin-Macrophage Hypothesis

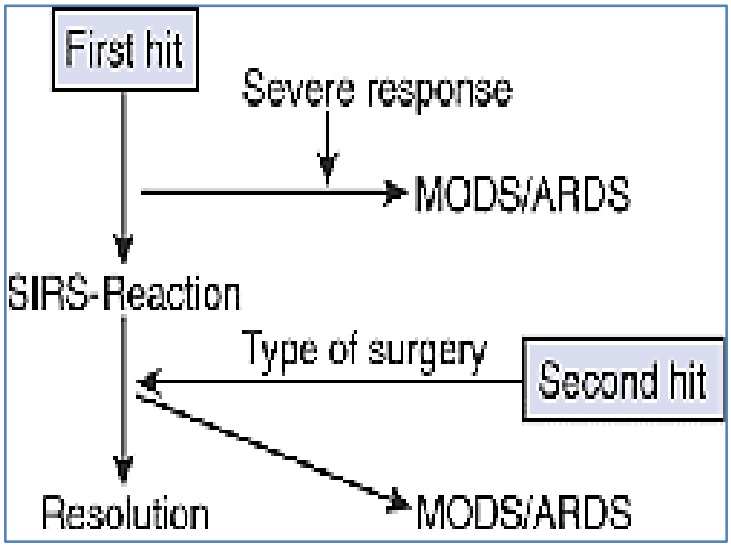
- In patients with MODS, infection with Gram-negative microorganisms is relatively common, so endotoxin has been proposed as a key mediator in this clinical syndrome.
- In this hypothesis, after the initial event (i.e., sepsis, pancreatitis, trauma), MODS develops as a result of production and liberation of cytokines and other mediators by endotoxin-activated macrophages.
- TNF-alpha, IL-1, IL-6, thromboxaneA_2, prostacyclin, PAF, and nitric oxide (NO) are the proinflammatory mediators that have been involved in the development of MODS .

Tissue Hypoxia-Micro vascularHypothesis :

- Micro and macro vascular changes results in hypoxia. Anemia , myocardial failure, hypoxemia, hypovolemiccauses decreased tissue oxygen delivery.
- Organ failure results from extensive thrombosis due to altered homeostasis.

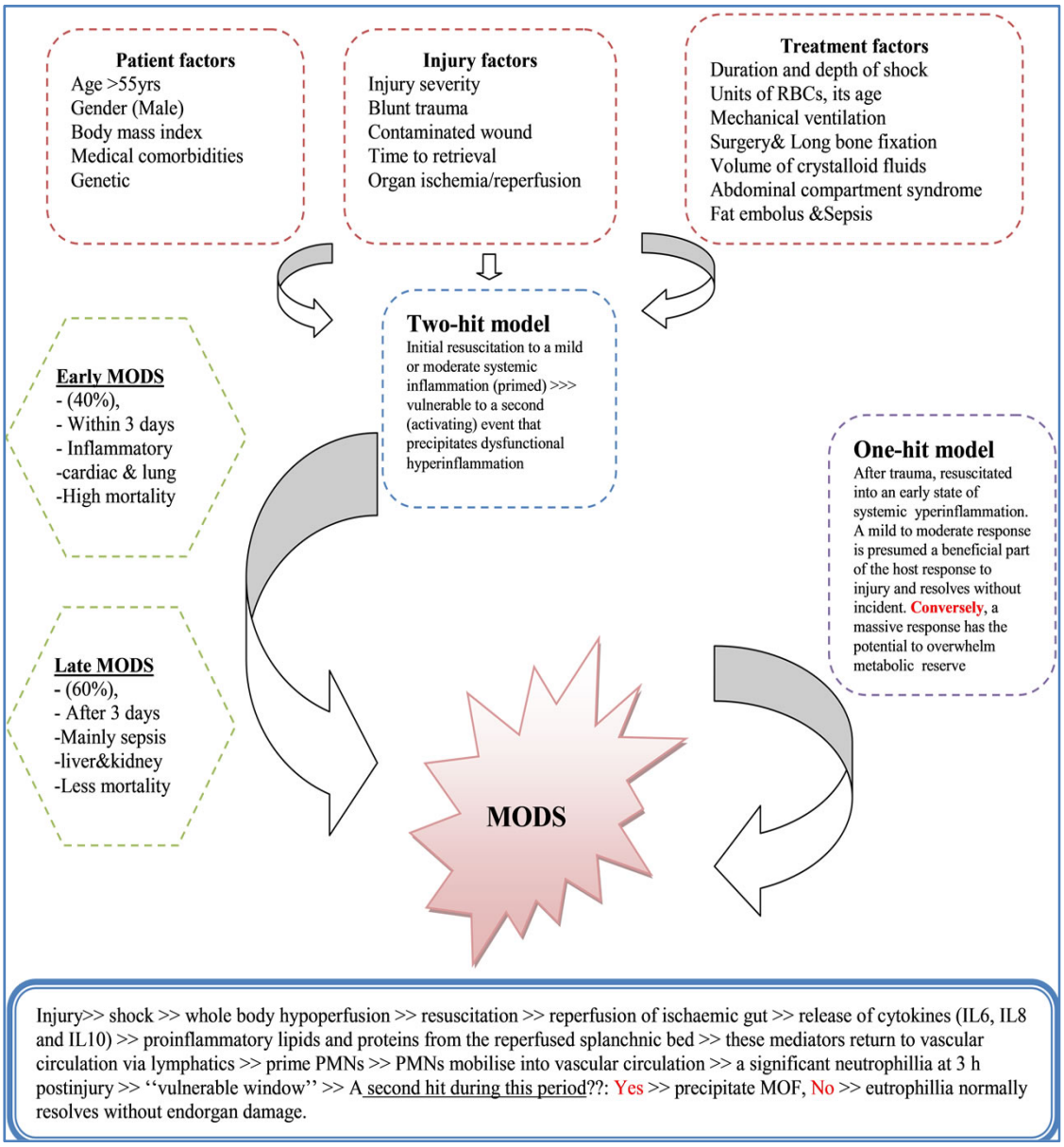
The Two-Event Hypothesis

- The two-event hypothesis concept says that first insult causes priming of the immune system. While the second injury results in severe response resulting in MODS



Integrated Hypothesis

- In most patients with MODS, the development of this syndrome cannot be traced to a single cause. It is likely that MODS is the end result of dysregulated hemostasis involving most of the mechanism cited above.



Diagnostic Criteria and Scoring Systems

There are about thirty different scoring systems described to diagnose and quantify the severity of multi organ dysfunction syndrome.

Prediction of outcome cannot be done by SOFA score.Quantification of complications in critically ill patients can be done using SOFA

SOFA score	0	1	2	3	4
Respirationa PaO_2/FIO_2 (mm Hg) SaO_2/FIO_2	>400	<400 221–301	<300 142–220	<200 67–141	<100 <67
Coagulation Platelets $10^3/mm^3$	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular[b] Hypotension	No hypotension	MAP <70	Dopamine </=5 or dobutamine (any)	Dopamine >5 or norepinephrine </=0.1	Dopamine >15 or norepinephrine >0.1
CNS Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200

Current Management Strategies

- The primary goal in the management of any critically ill patient must be to prevent the occurrence of a single organ failure and when possible specific corrective therapy of all identifiable risk factors for the development of MODS.
- The importance of maintaining adequate tissue perfusion in high-risk patients has been increasingly recognized. The level of perioperative tissue oxygen debt has been related to the postoperative incidence of MODS and patient outcome .
- It also has been shown that patients suffering from SIRS have an increase in oxygen consumption and an increase in resting energy expenditure, and more so, if the origin of SIRS is sepsis, suggesting that metabolic stress is greater in these patients.

SCORES

Sepsis is evaluated using various scoring systems like APACHE (Acute Physiological and Chronic Health Evaluation), SAPS II ,SOFA (Sequential Organ Function Assessment) etc.

APACHE II	APACHE II was designed to provide a morbidity score for a patient. It is useful to decide what kind of treatment or medicine is given. Methods exist to derive a predicted mortality from this score, but these methods are not too well defined and rather imprecise. APACHE II is an updated version.
SAPS II	SAPS II was designed to provide a predicted mortality, that does not reflect the expected mortality for a particular patient, but is good for benchmarking. In a rather simple way, it makes it possible to provide a single number that describes the morbidity of a number of patients.
SAPS III	SAPS III was designed to provide a realistic predicted mortality for a particular patient or a particular group of patients. It does this by calibrating against known mortalities on an existing set of patients, for a specific definition of mortality
SOFA	SOFA-Sequential Organ Failure Assessment was designed to provide a simple daily score that indicates how the status of the patient evolves over time.

GCS	Glasgow Coma Scale (also named GCS) is designed to provide the status for the central nervous system. It is often used as part of other scoring systems.
CMM	CMM - Cancer Mortality Model. To predict outcome of critical cancer patients.
MPM	MPM - Mortality Prediction Model .A model to assess risk of death at ICU admission. It has prediction models for assessment at admittance, 24h, 48h and 72h after.
RIFLE	RIFLE - Risk, injury, failure, loss and end-stage kidney classification. It has 3 severity levels (risk, injury and failure)
CP	CP - Child–Pugh: For patient with liver failure. Also used outside of the ICU.
Ranson score	simple score used specifically for patients with pancreatitis.
MODS	MODS Multiple Organ Dysfunction Score: with similar objectives as SOFA Score.

SAPS II

Its name stands for "Simplified Acute Physiology Score", and is one of several ICU scoring systems.

This scoring system is :

 Describe the morbidity and mortality of a patient when comparing the outcome with other patients.

 Describe the morbidity and mortality of a group of patients when comparing the outcome with another group of patients.

- It streamlines data collection and analysis without compromising diagnostic accuracy. The SAPS II is the most widely used version. It calculates a severity score using the worst values measured. Several of the variables (i.e., AIDS, metastatic cancer, hematological malignancy) are dichotomous, meaning that they are either present or absent.
- The others are continuous variables that have been made categorical by assigning points to ranges of values. As an example, a systolic blood pressure ≥200 mmHg is worth 2 points, 100 to 199 mmHg is worth 0 points, 70 to 99 mmHg is worth 5 points, and <70 mmHg is worth 13 points during the initial 24 hours in the ICU for 17 variables.

SAP III

Annex 1

Demographics/previous health status		Diagnostic category		Physiologic parameters on admission	
Parameters	Scores	Parameters	Scores	Parameters	Scores
Age		Scheduled admission	0	Glasgow	
< 40	0	Non-scheduled admission	3	3-4	15
≥ 40<60	5	Urgency		5	10
≥ 60< 70	9	Non-surgical	5	6	7
≥ 70< 75	13	Elective	0	7-12	2
≥ 75<80	15	Emergency	6	≥ 13	0
≥ 80	18	Type of surgery		Heart rate	
Comorbidities		Transplantation	-11	< 120	0
Others	0	Trauma	-8	≥ 120< 160	5
Chemotherapy	3	MR without valve	-6	≥ 160	7
ICC NYHA IV	6	Stroke surgery	5	Systolic blood pressure	
Hematologic neoplasia	6	Other	0	< 40	11
Cirrhosis	8	ICU admission add 16 points	16	≥ 40< 70	8
Aids	8	Reason for admission		≥ 70< 120	3
Metastasis	11	Neurologic		≥120	0
In-hospital days before ICU		Seizures	-4	Oxygenation	
< 14	0	Coma, confusion, agitation	4	Mechanical ventilation PaO_2/FiO_2 < 100	11
≥ 14-28	6	Focal deficit	7	Mechanical ventilation PaO_2/FiO_2 ≥ 100	7
≥ 28	7	Intracranial mass effect	11	Without mechanical ventilation PaO_2 < 60	5
Origin		Cardiologic		Without mechanical ventilation PaO_2 ≥ 60	0
Operating room	0	Arrhythmia	-5	Temperature	
ER	5	Hemorrhagic shock	3	< 34.5	7
Other ICU	7	Non-hemorrhagic hypovolemic shock	3	≥ 34.5	0
Others	8	Distributive shock	5	Leukocytes	
Vasoactive drugs		Abdomen		< 15,000	0
Yes	0	Acute abdomen	3	≥ 15,000	2
No	3	Severe pancreatitis	9	Platelets	
		Liver failure	6	< 20,000	13
		Others	0	≥ 20,000< 50,000	8
		Infection		≥ 50,000< 100,000	5
		Nosocomial	4	≥ 100,000	0
		Respiratory	5	pH	
		Others	0	≤ 7.25	3
				> 7.25	0
				Creatinine	
				< 1.2	0
				≥ 1.2-< 2.0	2
				≥ 2.0< 3.5	7
				≥ 3.5	8
				Bilirubin	
				< 2	0
				≥ 2< 6	4
				≥ 6	5
Total					

Adapted from Moreno RP. *Intensive Care Med* 2005; 31: 1345-55.

Chart 1 - Currently available and future perspectives for a PIRO based approach in sepsis

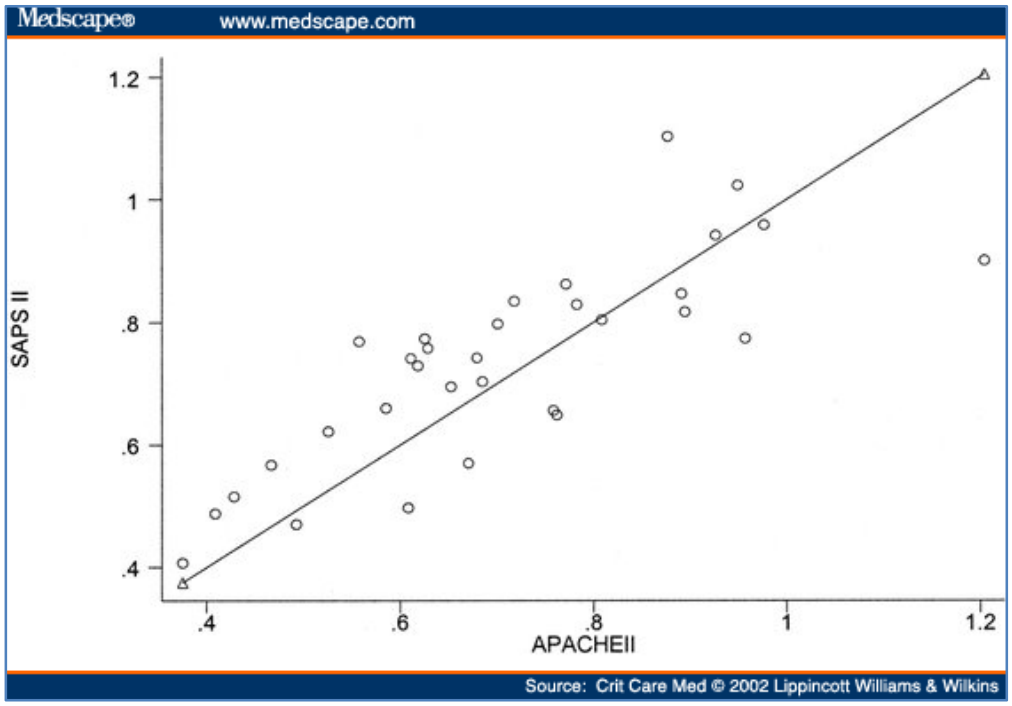
	P Predisposition	I Infection	R Response	O Organ dysfunction
Available	Age Comorbidities Chronic conditions Baseline severity Source of admission	Pathogen Susceptibility Bacteremia Bacterial load Site of infection Nosocomial or community-acquired infection	Clinical Resolution Hypoxemia Hypotension Immune Response	ARDS Shock Acute renal failure MODS SOFA
Future	Genetics Polymorphisms of toll-like receptor, tumor necrosis factor, IL-1 and CD14	Genotyping Assay of microbial products (LPS), mannan and bacterial DNA Detection of virulence factors	Biomarkers Nonspecific markers of activated inflammation (PCT or IL-6) or impaired host responsiveness (HLA-DR)	Mithocondrial dysfunction Endothelial damage and activation

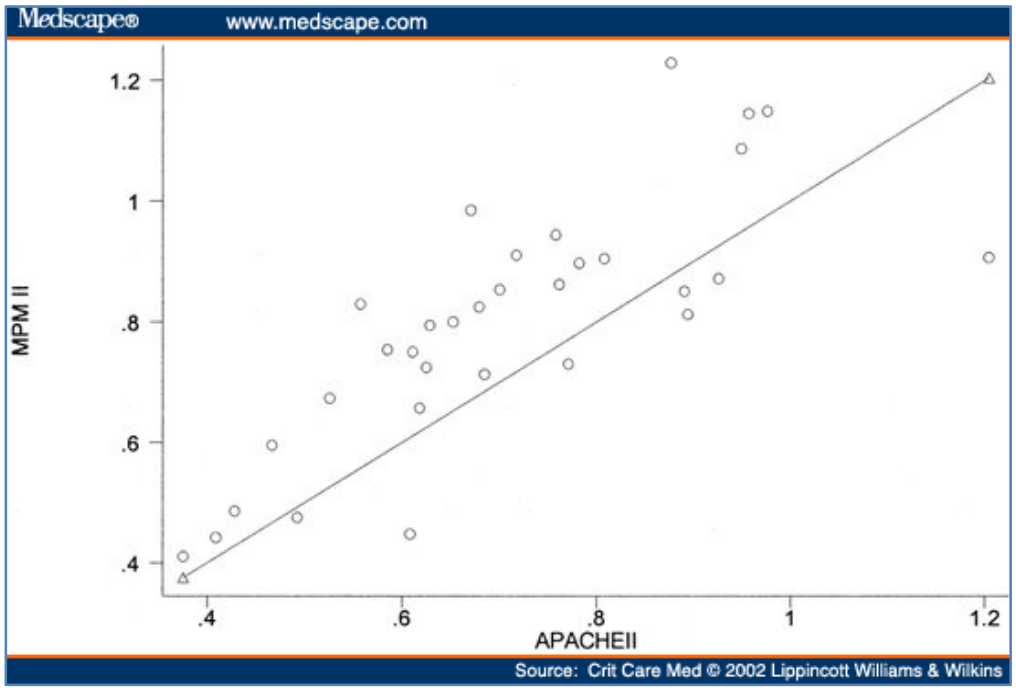
ARDS - Acute Respiratory Distress Syndrome; MODS - Multiple Organ Dysfunction Syndrome; SOFA - Sequential Organ Failure Assessment; PCT – procalcitonin; IL-1 – interleukin 1, IL-6 – interleukin 6; LPS – lipopolissacaride; DNA – dexoxiribonucleic acid; HLA-DR – D related human leukocyte antigens.

APACHE SCORING:

- APACHE is a reliable and useful means of classifying ICU patients. APACHE has also proved useful in evaluating outcome from intensive care and in comparing the success of different treatment . Original APACHE system was complex.
- APACHE system incorporates a four-letter (A, B, C,and D) designation corresponding to a spectrum ranging from excellent health (A) to severe chronic organ system insufficiency (D

APACHE II CORRELATED WELL WITH SAP II THAN WITH MPM II





- The APACHE II system is the result of efforts to simplify. The weights for the nine remaining physiologic variables used in APACHE II are the same as in the original APACHE system. Unlike APACHE, however, measurement of all 12 physiologic values is mandatory when using APACHE II**.** This eliminates the problem of missing values and concerns about the assumption that an unmeasured variable was normal .
- Although arterial blood gas measurements may be inappropriate for some patients, exclusion of these values is not encouraged and should only be done when clinical judgment strongly suggests the results would be within normal limits.
- Because severe chronic illness and age reflect decreased reserve they are added to APACHE II. Age is a very important risk factor associated with the mortality. It is found that when controlled for acute physiologic derangement and age, three of the four chronic health classifications (B,C, and D) were associated with higher death rates. However, only the most severe chronic organ system insufficiency or immunocompromised state (class D) markedly influenced outcome.
- Nonoperative and emergency surgery admissions have a substantially higher risk for death from their prior organ system insufficiency than elective

surgical admissions. (Surgery or postoperative patients are those admitted to the ICU directly from the operating or recovery room. All others are nonoperative.) This was probably because patients with the most severe chronic conditions are not considered to be candidates for elective surgery.

- Therefore, nonoperative or emergency operative admissions with a severe chronic organ system dysfunction are given an additional five points, while similar elective surgical admissions are only given two points. The maximum possible score is 71. There is no patient who has crossed 55.
- Description of the disease is combined with APACHE II score, especially for those diseases with a good overall prognosis (as indicated by a very negative coefficient, such as acute asthma or diabetic ketoacidosis) and those with a poor prognosis (corresponding to a large positive coefficient, such as septic shock)
- Classification would be more appropriate if done at an early point in time, such as in the emergency room or at the time of ICU admission. This would make the severity classification more independent from treatment.
- When the association between admission and worst-value APACHE II scores on a subset of GWUMC patients was tested, in 88% of the physiologic measurements the worst value over 24 h was the ICU admission

value. Also, 8 1 % of APS scores changed less than five points when using admission values only.

- However, although APACHE II scores based on admission values were close to those obtained using worst values over the initial 24 h, they were not identical. Therefore, many studies are in the process of further comparing initial values and worst 24-h values. Until this is completed, investigators must still use the worst value over 24 h.
- The ability to classify patient groups according to severity of illness will provide researchers with a new tool for improving the treatment of criticallyill patients.
- APACHE II can be very useful in clinicaltrials or in nonrandomized or multi-institutional studies of therapeutic efficacy. By providing a measure of severity of disease, APACHE II scores will help investigators determine whether control and treatmentgroups are similar.
- APACHE II predictions correlated well with the burns index. The use of the burn index has made it possible for investigators to demonstrate an overall improvement in the quality of burn care during the last decade. Similar comparisons would be possible for intensive care using APACHE II data collected over time.

- Like the Glasgow coma score,APACHE II should also be able to help determine whether new therapeutic interventions really benefit severely ill patients.
- In studies of specific disease groups, APACHE II scores can tell only less about the severity of disease. Additional indicators of severity, such as serum albumin and anergy testing for nutritional studies,or pulmonary mechanics for respiratory surveys can be used.
- The importance of APACHE II is that it combines in one summary measure the risk factors of physiologic derangement, age, and poor chronic health status. This is an improvement over the comparison of mean values which do not take into account comorbidity, interaction of variables from different organ systems, or important physiologic threshold.
- The original APACHE system demonstrates that the degree of physiologic derangement correlates closely with the need for admission and continued stay in an ICU for low-risk monitored patients.
- Because it is less complex and still relatively independent of therapeutic decisions, the APACHE II system should be even more useful for such questions or for determining the relative benefit of an invasive procedure. For specific research questions, it is suggested using only the 12 physiologic.

APACHE II

Physiologic Variable	High Abnormal Range					Low Abnormal Range				
	+4	+3	+2	+1	0	+1	+2	+3	+4	Points
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°	
Mean Arterial Pressure - mm Hg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49	
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39	
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5	
Oxygenation: A-aDO2 **or** PaO2 (mm Hg) a. FIO2 ≥0.5 record A-aDO2 b. FIO2 <0.5 record PaO2	≥500	350 to 499	200 to 349		<200 PO2>70	 PO2 61 to 70		 PO2 55 to 60	 PO2<55	
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15	
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110	
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6			
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20	
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1	
Glasgow Coma Score (GCS) Score = 15 minus actual GCS										
A. Total Acute Physiology Score (sum of 12 above points)										
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6										
C. Chronic Health Points (see below)										
Total APACHE II Score (add together the points from A+B+C)										

PROTEINURIA:

- Proteinuria designates the presence of elevated (nonphysiological) levels of proteins in urine (>200 mg/24 hr).During proteinuria the urine contains mainly of filtered plasma proteins and tubular Tamm-Horsfall proteins.The later is normal compound of urine produced mainly locally in the thick ascending limb of loop of Henle.
- Albumin is the main plasma protein, and an increased concentration of albumin in the urine is usually referred to as albuminuria. Even a small increase in urinary excretion of albumin (UAER), microalbuminuria (30 – 300 mg/24 h),is an early feature of many renal disease but is also established marker of endothelial dysfunction or the general health of vascular system.
- Micro albuminuria may also be a normal phenomenon, eg in strenuous physical exercise.it also seen in early diabetes, myocardial infarction. After trauma, knee and hip surgery microalbuminuria is significantly elevated. Low molecular weight proteinuria can occur in interstitial renal disease, such as in interstitial nephritis, lithium nephropathy, or unspecifically in Chronic kidney disease (CKD)(interstitial fibrosis).
- Some rare renal syndromes can also present with tubular, low molecular weight proteinuria. These syndromes include for example Dent's disease (CLC5-defect), Imerslund-Grasbeck syndrome (cubilin deficiency) , Lowe

syndrome and cystinosis, all due to deficient proximal tubular reabsorption (PTR).

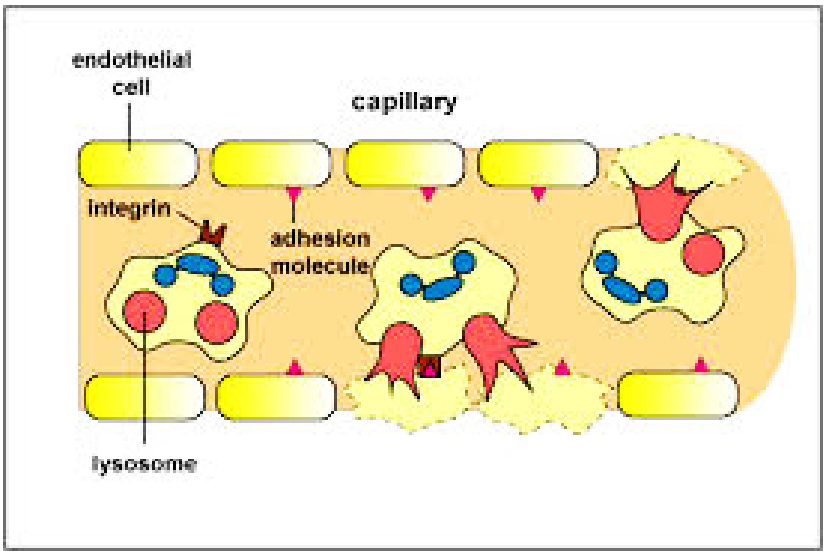
- Glomerular filtration of albumin is followed by tubular reabsorption (up to 98%) and thus albuminuria reflects the net result of these two processes together. Glomerular proteinuria is caused by a defect in the GFB. Characteristic for this type of proteinuria is that large plasma proteins that normally not are filtered, or only filtered to a limited extent, appear in the urine.
- Tubular proteinuria involves an impaired reabsorption of proteins by the tubular system. Smaller proteins that are freely filtered in the glomerulus and normally completely reabsorbed, can reach the urine when there is damage to the tubular system.
- Even for a normally functioning proximal tubule, tubular proteinuria can occur. Thus, when increasing amounts of proteins are filtered across the glomerular barrier they start to interface with the normal tubular reabsorption of low molecular weight proteins, competing for the binding sites on the receptors in the tubular system. This is generally called "overload proteinuria".
- Overproduction of various proteins, such as light chains in plasma in multiple myeloma, usually also produces a kind of overload proteinuria,

"Overproduction proteinuria" (Bence Jones proteinuria). Low molecular weight proteins are then, due to their increased plasma concentrations, filtered in higher amounts and when the tubular maximum is exceeded, thy appear in the urine.

Endothelial cells:

- Endothelial cells are coated, on the plasma side, by a negatively charged glycocalyx consisting of glycosaminoglycans and proteoglycans. Enzymatic degradation of glycocalyx of the glomerular capillaries results in increased permeability of the glomerulus to the albumin resulting in microalbumiuria.
- Glomerular capillaries are the vascular bed which are more susceptible to vascular injury. This is caused by activation of coagulation cascade by the endotoxin , release of tissue factor, fibrin deposition in the capillaries, and low fibrinolytic activity .
- In addition, activated neutrophils and a range of cytokines, such as IL-lb, TNF and platelet activating factor, are also implicated in the pathogenesis of endothelial injury. Acute renal failure occurs due to occurrence of micro thrombosis in the capillaries . It is well supported by human as well as experimental studies.

ENDOTHELIAL CELL DYSFUNCTION



MICROALBUMIURIA

- Because of high permeability of albumin in the glomerulus ,there is leakage of small amount into the urine resulting in microalbuminuria. The term microalbuminuria has been replace by KIDIGO as moderately increased albuminuria..
- The tubular reabsorptive mechanism for albumin from the ultra-filtrate is exceeded beyond its threshold capacity, leading to increased excretion of albumin in the urine. The degree of albuminuria is dependent on the intensity of the inflammatory responses, and therefore micro albuminuria reflects disease severity found to be prevalent in a broad spectrum of critically ill patients.

Pathophysiological changes in the kidney associated with albuminuria

- There are few changes in the microvasculature of kidney. Several hypothesis have been suggested . They are,

Hypothesis 1

- Glomerular permeability is changed
- Proximal tubular reabsorption is decreased.

Hypothesis 2

- It is due to generalised endothelial dysfunction.
- Glomerular barrier is affected.
- Tubular metabolism and reabsorption are impaired.
- Reduction in basement membrane negative charge due to loss of proteoglycan.
- Pore size is increased.
- Heparansulfate plays a major role . It not only maintains the electro negativity but also maintains the pore size thus preventing micro albuminuria.
- Other mechanism includes podocyte dysfunction affecting the filtration barrier.

- Mesangial cell growth is inhibited by heparin sulphate . In DM there is mesangial expansion and reduced filtration suface area.
- Increase in filtered albumin cause renal dysfunction .Increased load on the tubules to absorb albumin may result in interstitial inflammatory injury and result in renal dysfunction.
- Micro albuminuria was the reason for increased incidence of mortality in critically ill patients. It is probably the result of widespread endothelial dysfunction arising from the effects of cytokines, and other inflammatory mediators, released during the intense inflammatory responses that are associated with critical illness.
- The effects of disruption of the integrity of the endothelial barrier is manifested as altered glomerular endothelial permeability in the kidneys, allowing increased amounts of albumin to escape into the glomerular ultra-filtrate.
- The tubularreabsorptive mechanism for albumin from the ultra-filtrate is exceeded beyond its threshold capacity, leading to increased excretion of albumin in the urine.
- The degree of albuminuria is dependent on the intensity of the inflammatory responses, and therefore micro albuminuria reflects disease severity found to be prevalent in a broad spectrum of critically ill patients.

- The final common pathway for micro albuminuria is increased endothelial permeability which occurs due to various mediators, like neutrophil ,macrophage, complement activation, and endothelial stimulation resulting in inflammatory injury.

Sample		Lower level	Upper levels	Unit
24h		30	300	mg/24h
Short-time		20	200	µg/min
Spot		30	300	mg/L
Spot urine ACR		3.5	35	mg/mmol
		30	300	µg/min

- The glomerular manifestation of sepsis is microalbuminuria. Microalbuminuria is a marker of endothelial dysfunction. The traditional method of 24-h urine samples collection for detection of microalbumiuria is cumbersome and it takes a lot of time . It may result in collection errors and poor compliance.

- Immunonephelometricmethod ,ELISA , Radial immunodifussion, immunoturbidmetric method and radio immno assay have been used for the albumin measurement in urine.

Review of assays to assess albuminuria

Method	Detection limit
Immunonephelometry (Beckman Coulter Array analyzer)	2 mg/L
Immunoturbidimetry (Dade Behring turbimeter)	6 mg/L
Hemocue (point of care)	5 mg/L
Radioimmunoassay	16 µg/L

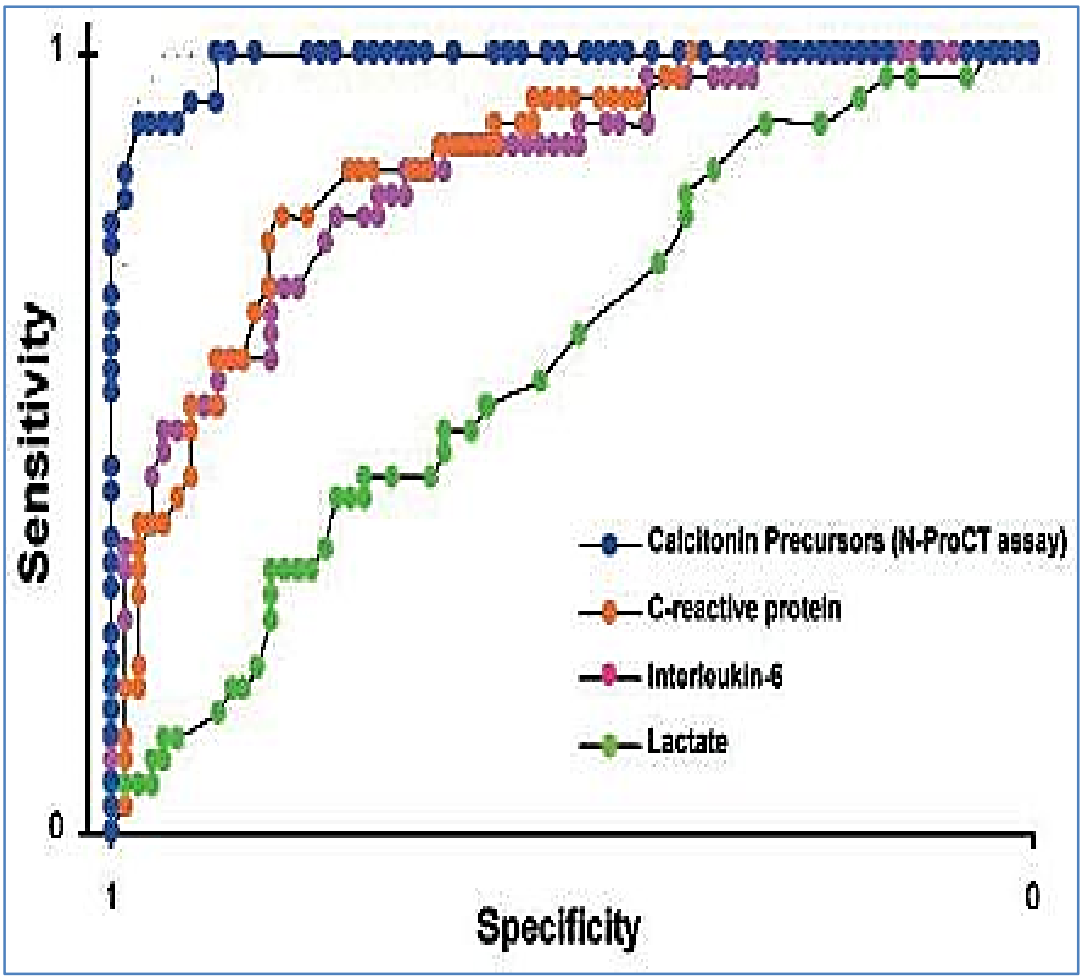
- The presence of microalbuminuria occurs very early in the onset of inflammatory process in sepsis and it persists in complications of sepsis. urinemicroalbumin occurs within the first first six hours following ICU admission.
- The microvascular effects of systemic inflammation can be monitored by serial measurement of microalbumin in urine.
- Microalbuminuria is better indicator than Acute Physiological and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Function Assessment score (SOFA score) in predicting vasopressor requirement and mortality.

- Occurrence of microalbuminuria correlated with the other biomarkers of sepsis like procalcitonin (PCT), CRP and cell adhesion molecules. Cell adhesion molecules are involved in the pathogenesis of endothelial injury resulting in MODS.

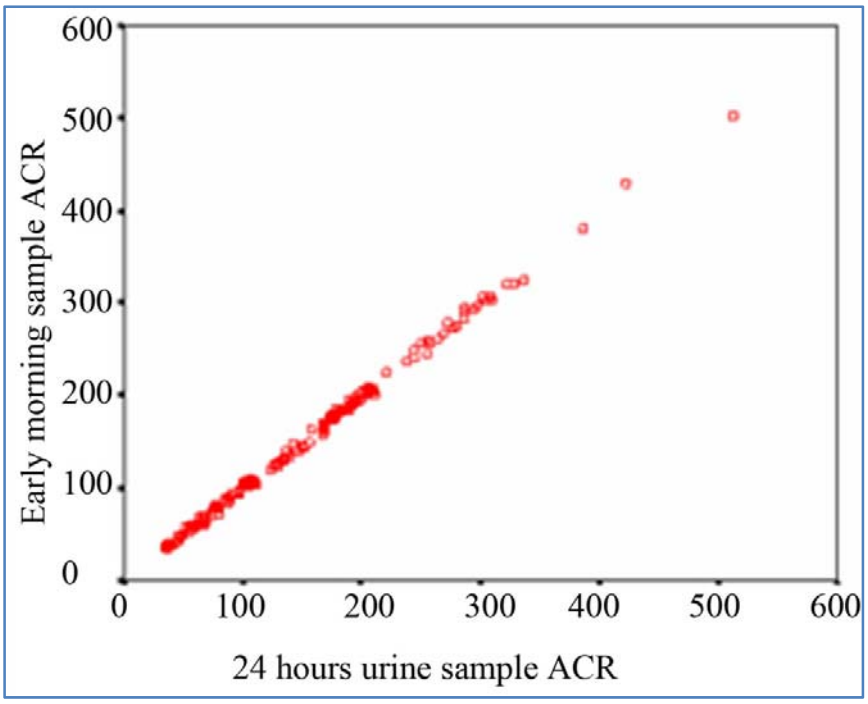
- Intercellular adhesion molecule-1, Endothelial leukocyte adhesion molecules and vascular cell adhesion molecule-1 are the cell adhesion molecules raised during systemic inflammatory response syndrome. Cell adhesion molecules are elevated in patient with sepsis when compared with patients who suffered trauma.

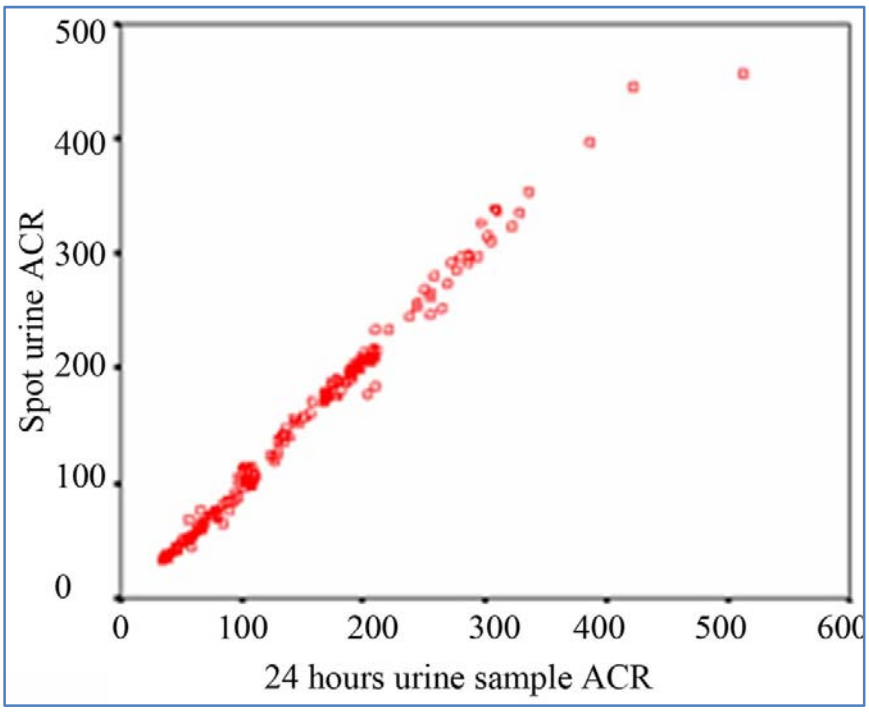
- C- reactive protein does not correlate with the severity the disease and it is not specific and has a very slow induction time.

- Procalcitonin has a lot of advantages over C- reactive protein. It has more specificity and sensitivity compared to C- reactive protein. But the induction time of procalcitonin is slower than microalbuminuria.



- Endothelial dysfunction may occur in many aseptic conditions which are not due to sepsis. It is not known whether there is difference in the degree of microalbuminuria in sepsis when compared to non infectious insults like burns , pancreatitis, trauma, myocardial infarctionetc.

- 



Early morning ACR correlates better than spot ACR with the 24 hr ACR.

- Thorevska N et al conducted a study to ascertain the significance of urine microalbumin in evaluating the prevalence, predictors and prognosis of critically ill medical patients.
- In 104 critically ill patients, microalbuminuria or proteinuria was present in 60% of patients and the albumin creatinine ratio of more than 100 mg/gm was observed in 43.3%. The median APACHE II score was observed as 20.5% and the median SOFA score was 5.0.Tere is 26.9% overall mortality rate in this study.
- In critically patients there is high prevalence of microalbuminuria and the risk of mortality in 2.7 times higher in patients with ACR >100 mg/gm compared to others.69% patients had microalbuminuria or proteinuria on admission and 43.3% had ACR >100mg/gm.Median APACHE II and SOFA score was 20.5 and 5.0.Overall mortality rate was 26.9%.
- He concluded that the prevalence of microalbuminuria is high in critically ill patients and ACR is more than 100 mg/gm were 2.7 times increased risk of mortality when compared to patients with ACR<100 mg/gm.[70]
- A study done by Gopal S et al concludes that microalbuminuria is an independent predictor of severity of illness and mortality in ICU patients.[71]

- A study done by Abid et al to assess the microalbuminuria as a predictor of the development of multiple organ dysfunction (MODS) and acute respiratory failure (ARF) in ICU patients.
- Patients in this study were divided into 2 groups. Patients with increased level of microalbumin in 48 hours from 5.2 mg/dl ± 2.0mg/dl to 19mg/dl ± 3.0mg/dl are included in group 1. Patients with decreased level of microalbumin in 48 hours from 16.4mg/dl ± 4.8mg/dl to 7.8mg/dl ± 3.0mg/dl are included in group 2.Group 1 had higher mortality rate (43%) when compared to other group ($p<0.05$).The higher SOFA score and APACHE II score were observed in group 1(43%) when compared to other group. The increasing value of urine microalbumin has 100% negative predictive value for the development of ARF and 96% for MODS.[72]
- Todi et al conducted a study in critically ill patients to evaluate the degree of urine microalbumin to predict the diagnosis of sepsis. Concluded that absence of significant microalbuminuria is unlikely to be associated with sepsis without significant microalbuminuria.[73]
- Study conducted by Basu et al to find out the correlation of degree of urine microalbumin in patients with sepsis and non-sepsis and to predict the mortality in critically ill ICU patients. Patients in this study were

divided into 2 groups. Patients with sepsis were included in group 1 and those without sepsis were included in group 2.

- The median ACR -1 (ACR on admission) was higher (206mg/gm,IQR 129.7 – 506.1) in group 1, compared to the other group (76.4mg/gm,IQR 29 – 167.1), p-value =0.0016.The discrimination between sepsis and non sepsis may be made at a cut-off value of 124mg/dl with 80% sensitivity,64.1% specificity,30% positive predictive value and 87.3% negative predictive value.
- The median ACR II (at 24 hours of admission) (154mg/gm,IQR 114 – 395.3mg/gm) was higher in non-survivor than survivor (50.8mg/gm,IQR 21.6 – 144.7mg/gm). The cut-off value of 99.6mg/gm could predict mortality with sensitivity – 68% negative predictive value – 97%,positive predictive value of 30%.
- It is unlikely that patient without significant microalbuminuria has sepsis.Abscence of elevated microalbuminuria at 24 hours of admission has high predictive value for survival, which is comparable to APACHE II score.[74]
- A study conducted by Makris et al evaluated the significance of micro albuminuria as an early marker of endothelial dysfunction that accompanies Systemic Inflammatory Response Syndrome. He concluded

that there is a significant correlation between microalbuminuria and organ dysfunction.

- A study undertaken by Berton G et al(2000)found that Albumin Excretion Ratio (AER) increases during Acute MI and that it correlates with the prognosis.[75]
- Similar study conducted on patients with sub arachnoid haemorrhage by Terao Y et al found microalbuminuria in the sub arachnoid haemorrhage patients was associated with poor prognosis.[76]
- A study done by gosling et al(2003)found that mortality was associated with microalbuminuria. P value was 0.0002 when compared between the survivors and non survivors. P value was 0.0021 for the association between hospital stay and microalbumiuria. P value was significant for the association between serum creatinine, CRP and bilirubin.[77]

METHODOLOGY

STUDY: STUDY OF MICROALBUMINURIA IN SEPSIS WITH REFERENCE TO APACHE II SCORE

Source of data :

The study was conducted on patients admitted to medical ICU/Medical emergency ward, Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai after getting ethical committee approval.

Method of data collection:

a) Studydesign:Prospective, on-interventional study in a tertiary care hospital.

b) Sample size: 50

c)Samplemethod:Simple random sampling.

d)Duration of study: 6 months.

e)Method of collection of specimens and processing:

- Spot urine sample was collected within 6 hours and at 24 hours of admission to medical emergency/ICU ward. Sample tested for urine micro albumin by using immunoturbidometric method and for urine creatinine by jafee method. Urinealbumin: creatinine ratio was calculated. (At 6 hours ACR-1 and at 24 hours ACR-2).

- APACHE II scoring was done at 24 hours of admission. Patientswasfollowed up during the course of hospital stay and the outcome of the patient (i.e. Death/Survival) is recorded.

f) Inclusion criteria:

- Patients admitted to medical emergency ward/medical ICU in Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai**,** with features of SIRS (systemic inflammatory response syndrome) and suspected infection .

Systemic inflammatory response syndrome(SIRS):

Presence of two or more of the following:

- Fever(oral temperature more than 38^0C) or hypothermia(less than 36^0C).
- Tachycardia(heart rate more than 90 beats per min).
- Tachypnea(more than 24 beats per min).
- Leukocytosis(more than 12,000/μL), leukopenia(less than 4.000/μL) or presence of more than 10 percent bands.

g)Exclusion criteria:

- Diabetes Mellitus
- Systemic hypertension

- Patients with preexisting chronic kidney disease/Patients with proteinuria due to renal/post renal causes
- Patients with preexisting urinary tract infection
- Patients receiving nephrotoxic drugs
- Patients with urologic trauma resulting in frank hematuria or urinary tract infection
- Anuria
- Pregnancy/menstruation
- Patients less than 16 years

h) Investigations:

- White blood count(total count & differential count)
- hemoglobin
- platelet count
- Blood urea
- serum creatinine
- Serum electrolytes
- Random blood sugar
- Liver function test
- Fasting blood sugar,
- post prandial blood sugar

- Urine culture sensitivity
- Blood culture sensitivity
- Sputum culture sensitivity(if needed)
- Arterial blood gas analysis
- Chest X ray
- ECG/USG KUB/Abdomen(if needed)
- CSF analysis(in suspected meningitis)

Data was collected using a pre tested proforma meeting the objectives of the study. Detailed history, physical examination and necessary investigation wasundertaken. The purpose of the study was explained to the patient and informed consent obtained. Patient was followed up during the course of the hospital stay and the outcome of the patient (i.e.death/survival) is recorded.

Data Analysis and interpretation:

Data was entered into Microsoft excel and analysis were done using the statistical Package for Social Sciences (SPSS) for windows software (version 18.0;SPSS Inc, Chicago).The chi-square test and fisher's exact test was used to

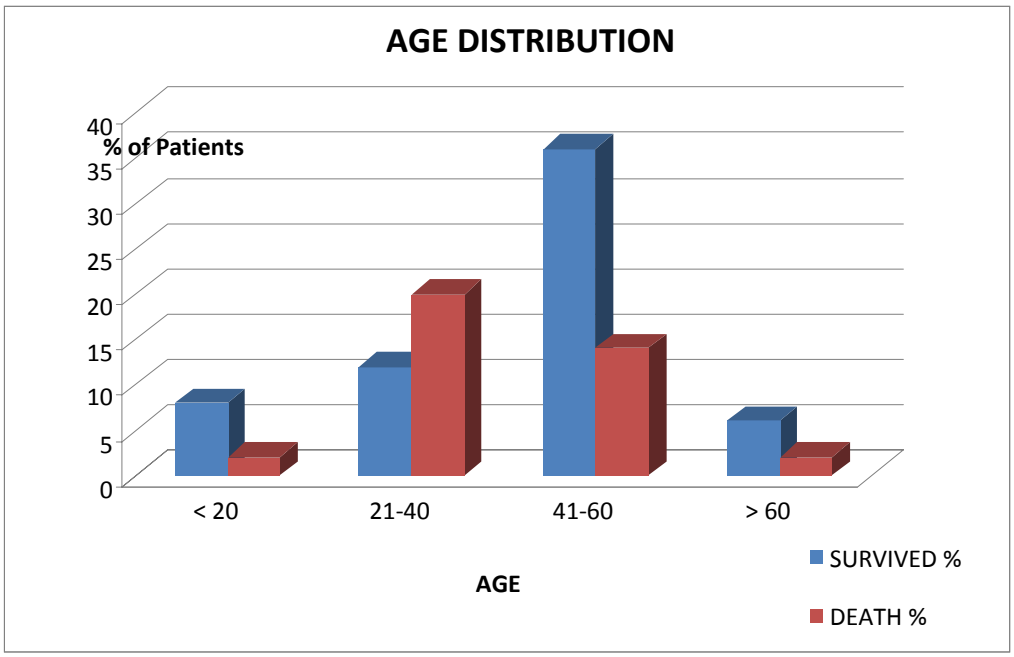
show the associations between predictor and outcome variables. The level of significance was set at 0.05.

OBSERVATION AND RESULTS

Distribution of patients according to age group

AGE IN YEARS	DEATH		SURVIVED		TOTAL	
	No.	%	No.	%	No.	%
< 20	1	2	4	8	5	10
21-40	10	20	6	12	16	32
41-60	7	14	18	36	25	50
> 60	1	2	3	6	4	8
TOTAL	19	38	31	62	50	100
MEAN	43.5 ±15.8					
RANGE	16-85					

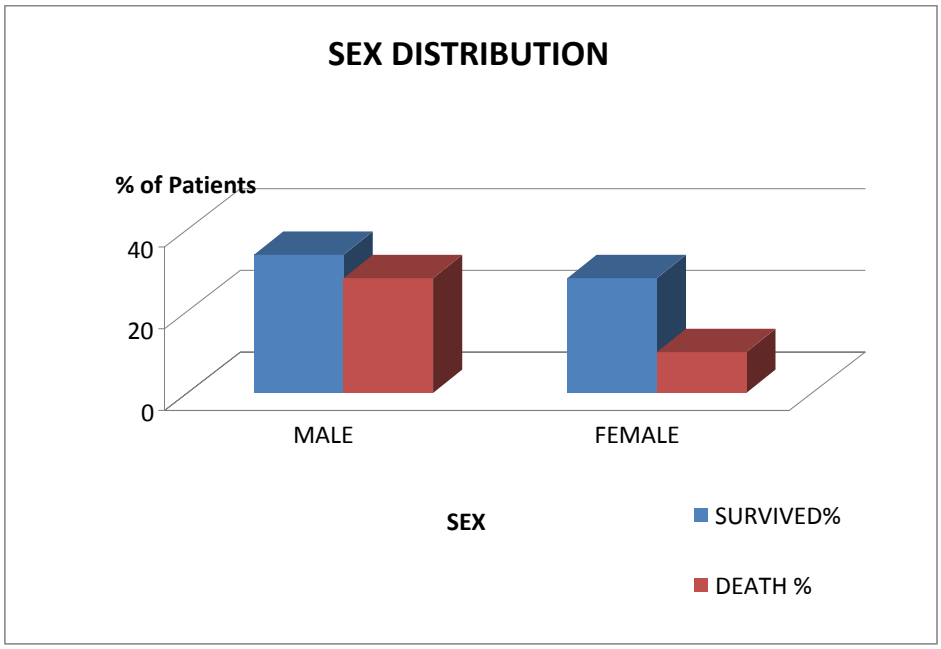
In this study the lowest age in this group of patients was 16 Years and the highest age in this group was 85 Years. The mean age of the study group was 43.5 with the SD of 15.8.



Distribution of patients according to age group

sex	DEATH		SURVIVED		TOTAL	
	No.	%	No.	%	No.	%
MALE	14	28	17	34	31	62
FEMALE	5	10	14	28	19	38
TOTAL	19	38	31	62	50	100

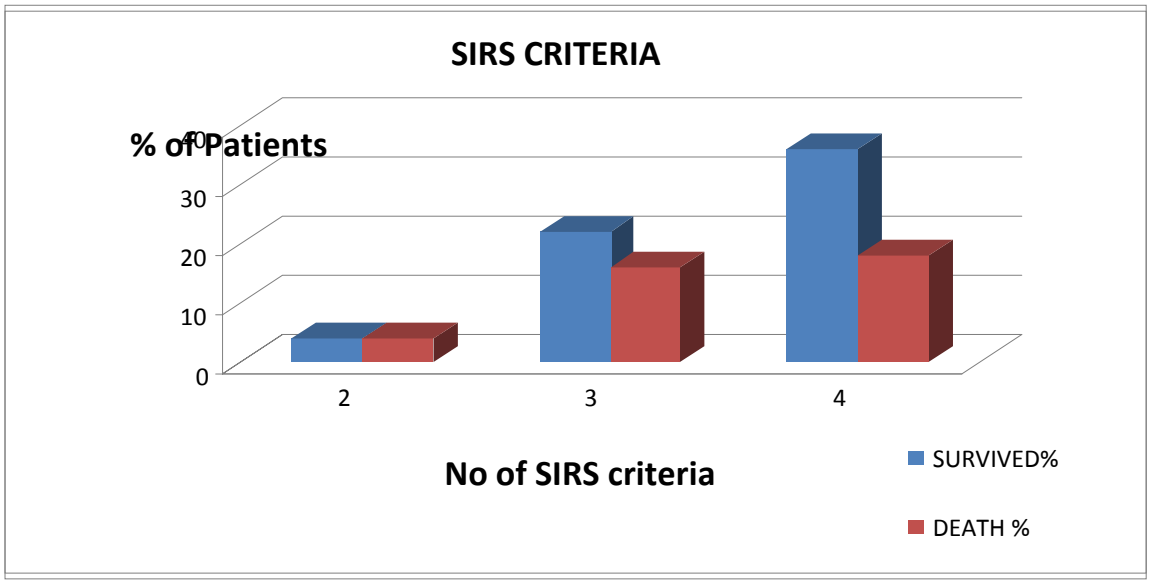
In this study out of 50 patients, 19 were female(38%) as compared to 31 male (62%).Among the 19 Non Survivors 5 were female (26.21 %) and 14 were male (73.68%). Among the 31 survivors 14 were female.



Distribution of patients according to no of SIRS criteria

NO OF SIRS CRITERIA	DEATH		SURVIVED		TOTAL	
	No.	%	No.	%	No.	%
2	2	4	2	4	4	8
3	8	16	11	22	19	38
4	9	18	18	36	27	54
TOTAL	19	38	31	62	50	100

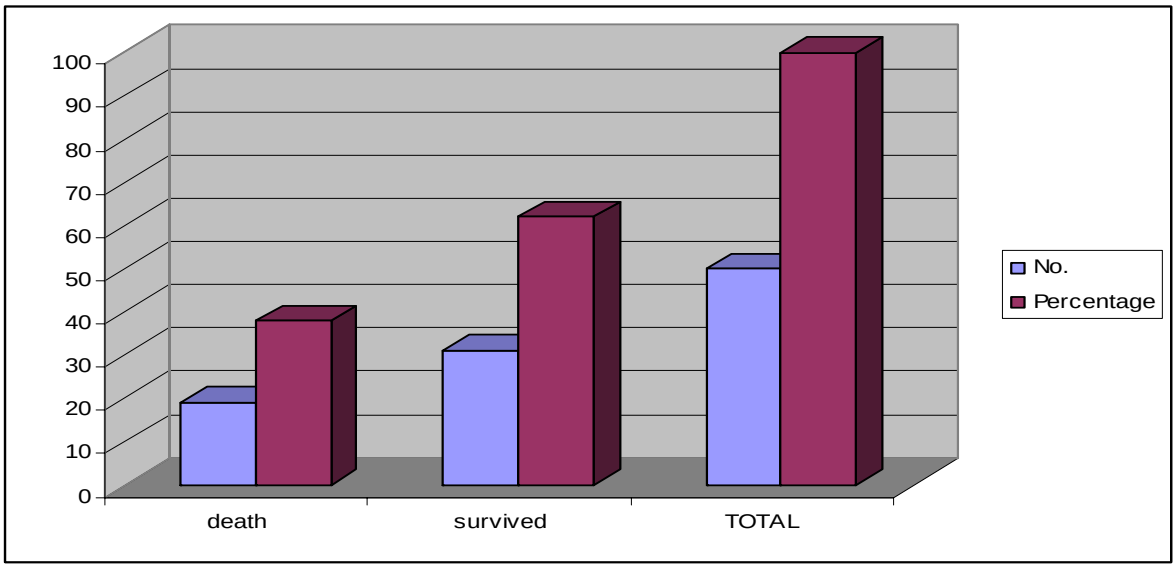
In this study out of 50 patients 27(54%) patients had all the four criteria for SIRS and 19 patients (38%) had three criteria of SIRS and 4 patients (8%) had only two criteria.The mortality rate for the patients who were having four criteria of SIRS was 33.33%. and who were having three criteria of SIRS were 42.1%.



Distribution of patients according to outcome

Outcome of the Patient	No	Percent
Death	19	38
Survived	31	62

In this study out of 50 patients 19 patients(38%) were not survived and 31 patients(62%) servived.

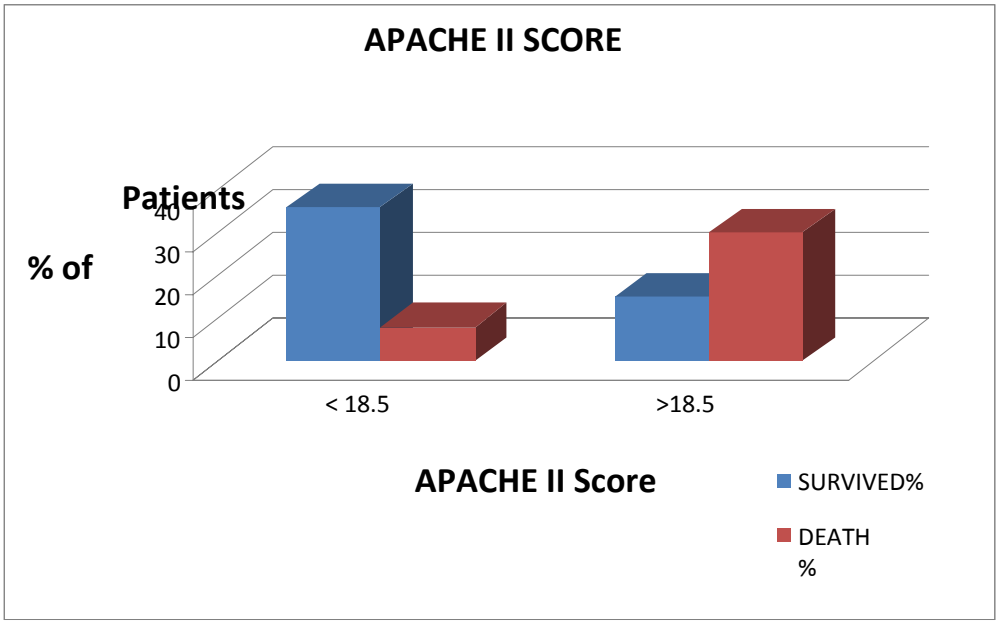


Distribution of patients according to APACHE II score

APACHE II	DEATH		SURVIVED		TOTAL	
	No.	%	No.	%	No.	%
< 18.5	4	8	19	38	23	46
>18.5	15	30	12	24	27	54
TOTAL	19	38	12	62	31	62
MEAN	25.47±6.93		16.35±6.78		19.82±8.11	
RANGE	6 – 37					
P Value	<0.0001					

In this study out of 50 patients APACHE II score ranged from 6 to 37 with a mean value of 19.82(SD±8.11). Out of 36 patients who had APACHE II score of more than 18.5, 15 patients died (55.55%), when compared to patients who had APACHE II score of less than 18.5, four patients died (17.39%)

The mean APACHE II score among t he survivors was 16.35 with Standard Deviation of 6.78, when compared to the mean value of non survivors was 25.47 with Standard Deviation of 6.93 .As the P value was <0.0001, hence it was statistically significant.


APACHE II SCORE
% of Patients
40
30
20
10
0
< 18.5
>18.5
APACHE II Score
SURVIVED%
DEATH %

Distribution of patients according to urine ACR 1

ACR 1	DEATH		SURVIVED		TOTAL	
	No.	%	No.	%	No.	%
< 109.5	3	6	31	62	34	68
>109.5	16	32	0	0	16	32
TOTAL	19	38	31	62	50	100
Mean	164.53±46.61		74.06±20.83		108.44 ± 55.05	
Range	33 – 245					
P Value	< 0.001					

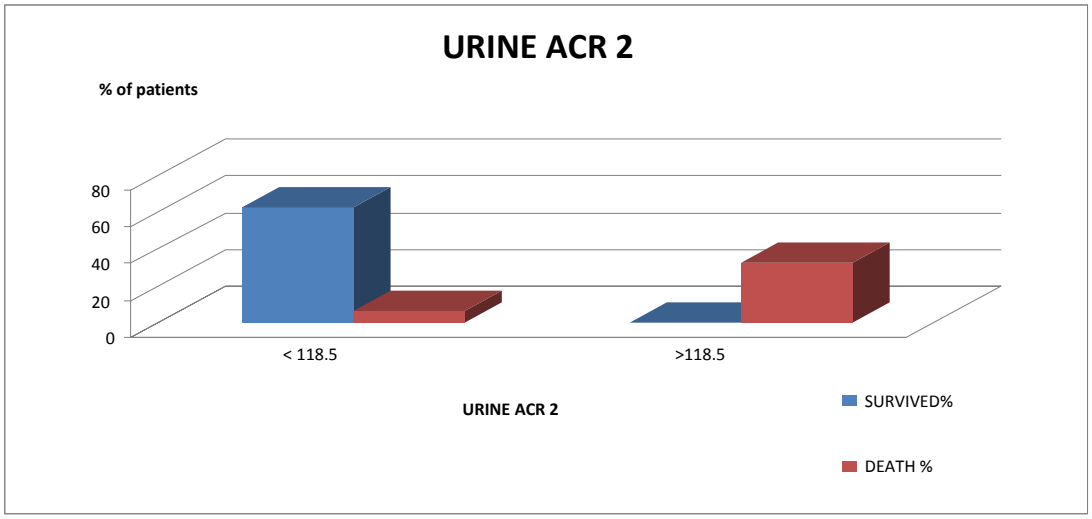
In this study out of 50 patients Urine Micro Albumin Creatinine Ratio done on admission ranged 33 to 245 microgram/mg.

Out of 16 patients (32%) who had ACR 1 value more than 109.5, all the 16 patients died.Out of 34 patients (68%) who had ACR 1 value less than 109.5, three patients died (8.82%).There is statistically significant P value of < 0.0001.

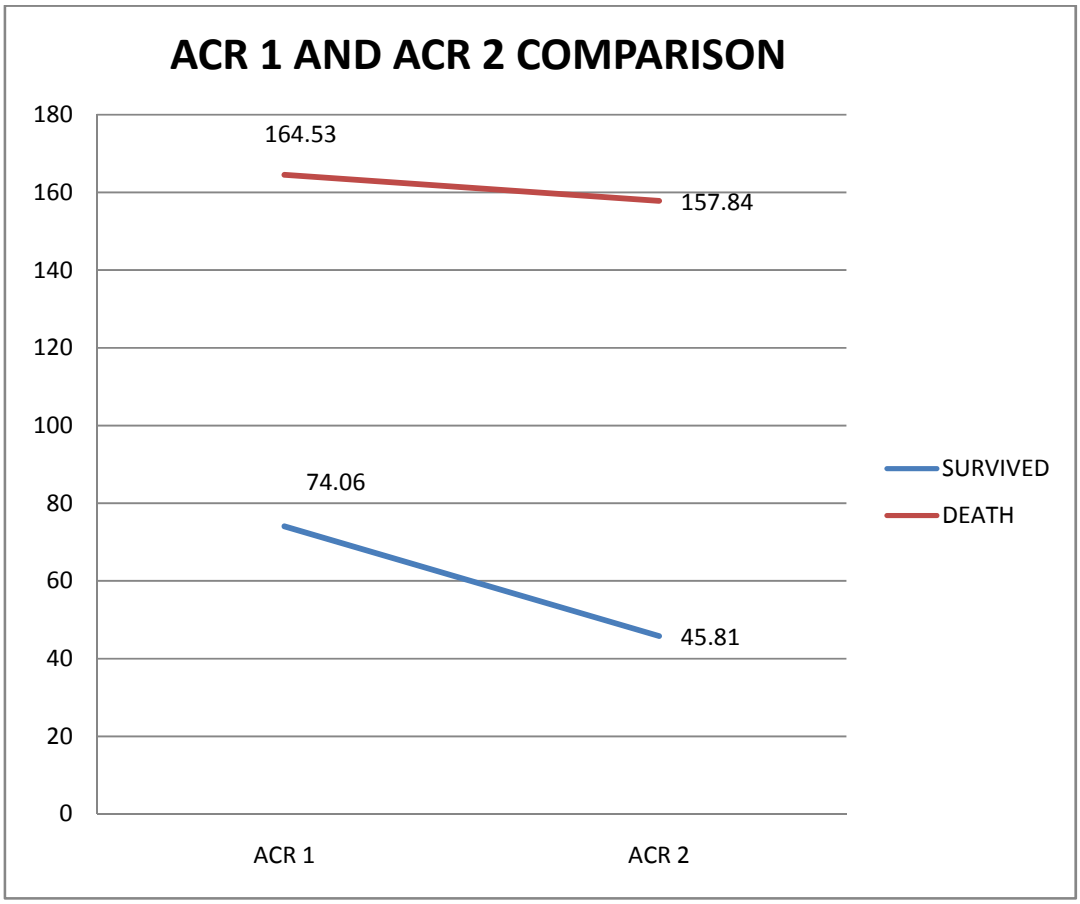
Distribution of patients according to urine ACR 2

ACR 2	DEATH		SURVIVED		TOTAL	
	No.	%	No.	%	No.	%
< 118.5	3	6	31	62	34	68
>118.5	16	32	0	0	16	32
TOTAL	19	38	31	62	50	100
Mean	157.84±36.96		45.81±17.92		88.38±60.96	
Range	15 – 221					
P Value	< 0.001					

In this study out of 50 patients Urine Micro Albumin Creatinine Ratio done at 24 hours of admission ranged 15 to 221microgram/mg. Out of 16 patients (32%) who had ACR 2 value more than 118.5, all the 16 patients died.Out of 34 patients (68%) who had ACR 2 value less than 118.5, three patients died (8.82%).There is statistically significant P value



Comparison of urine ACR 1 AND urine ACR 2 amoung surviour and non-surviour



Urine ACR 1 WAS 74.06 µgm/mg amoung surviours and 164µg/mg amoung non surviours and ACR 2 was 45.81 µg/mg amoung surviouras and 157 µg/mgamoung non surviours.both were statistically significant with p value <0.0001.

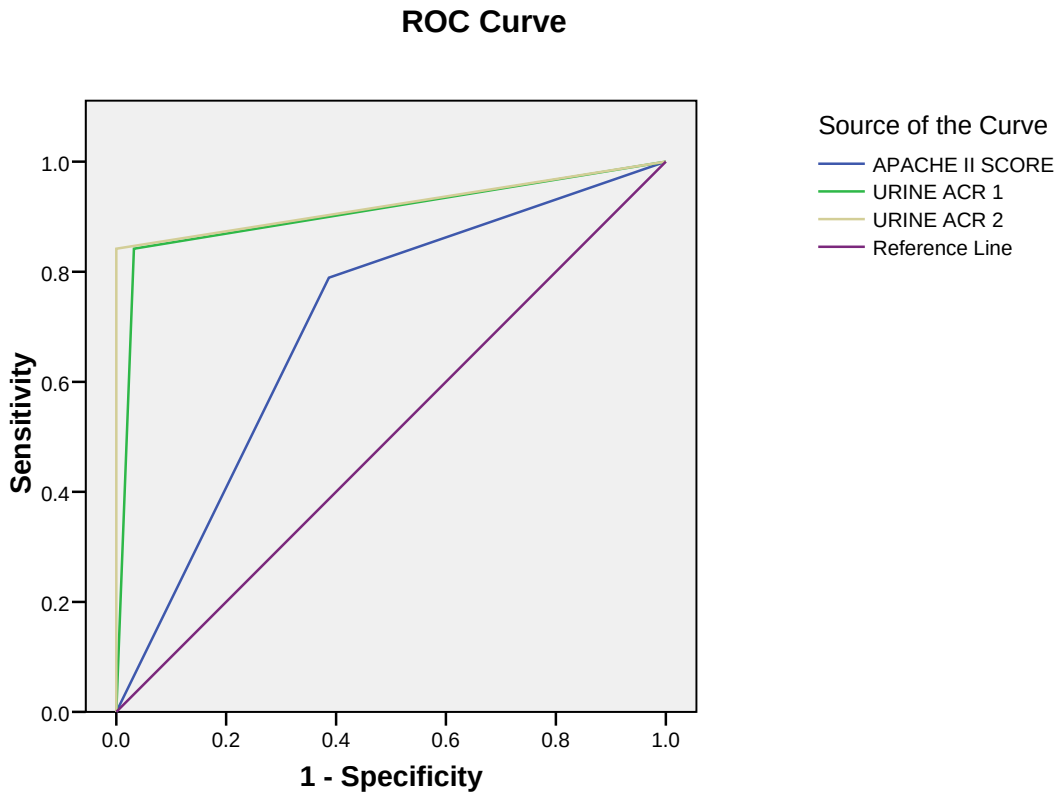
Co-relation between Micro-Albuminuria and APACHE II score

	Mean	Standard Deviation
APACHE II SCORE	19.82	8.113
URINE ACR 1	88.38	60.960
URINE ACR 2	108.44	55.055

Co-relation	Co-relation Co-efficient	P value
Urine ACR 1 and APACHE II score	0.809	<0.0001
Urine ACR 2 and APACHE II score	0.726	<0.0001
Urine ACR 1 and Urine ACR 2	0.912	<0.0001

There is good co-relation between Urine ACR 1 and APACHE II score. The P value is <0.0001, which is statistically significant.

Comparison of Area under curve for APACHE II Score,ACR1 and ACR 2 in predicting mortality



Diagonal segments are produced by ties.

Test Result Variable	Area Under Curve
APACHE II score	0.701
URINE ACR 1	0.905
URINE ACR 2	0.921

The area under curve was Larger for Urine ACR 2 (92%), when compared to APACHE II score (70%). Urine ACR 1 (AUC 90.5%) also has comparable value with ACR 1 value. This implies, ACR 2 and ACR 1 had better correlation with the mortality of the patients when compared to APACHE II score.

DISCUSSION

1) AGE

Patients were distributed from age 15 to 85 years with age >60 years constituting 8%.Mean age of the study population was 43.5 years (SD 15.8).

A study conducted by S Todi et al (2010) showed mean age of 58.17 years (SD 18.66) and a study done by Angus DC et al showed mean age of 57.0[8] .Patients with age > 60 years constituted 34.8% of the study population.[73]

2) SEX

In the present study 19 patients (38%) were female and 31 patients were male (62%).In a study conducted by S Todi et al in India which studied epidemiology of sepsis in which male patients constituting 57.71%.[73] study done by Angus DC et al [78] showed male patients constituted 51.9% and the study done by S Sreedharan et al showed male patients constituted 60.5%. This study shows that sepsis is more common among males compared to females.[79]

Comparision of sex distribution of patients with other studies.

Study	Angus DC et al	S todi et al	Study S sreedharan et al	Present study
% male	51.9%	57.71%	60.5%	57.81%
%female	48.1%	42.29%	39.5%	38%

3) CO-MORBID ILLNESS

In this study done out of 50 patients, 4 patients (8%) had COPD and patients (5%) had systemic hypertension, 4 patients had (8%) had Decompensated Chronic Liver Disease (DCLD) and 4 patients (8%) were Immunocompromised (HIV). A study done by Angus DC et al[78] showed that COPD was the most common underlying co-morbidity which was present in 12.3% of the patients.

4) SIRS CRITERIA

In the present study 27 patients (54%) had all the 4 criteria for SIRS, 19 patients (38%) had 3 criteria and 4 patients (8%) had 2 criteria.

5) ORGAN DYSFUNCTION

Cardiovascular system: 33 Patients (66 %) had cardiovascular system dysfunction in the form of MAP < 70 mmHg, mean ACR1 and ACR2 were 116.45

μg/mg and 101.09 μg/mg among patients with cardiovascular dysfunction and 92.88 μg/mg and 63.7 μg/mg amoung patients with no cardiovascular dysfunction. P value was statistically significant.

Renal system: 19 patients(38%) had renal dysfunction in the form of urine output <0.5L/24 hr. Median ACR1 and ACR2 were 102 μg/mg and 84μg/mg among patients with renal dysfunction and 88 μg/mg and 53 μg/mg among patients with no renal dysfunction.P value was statistically significant.

Haemotologic system: 7 patients (14 %) had haematologic dysfunction in the form of platelet count <80000/cumm.

6) MORTALITY

Mortality percentage in this study was 38%.This is consistent with various studies including study done by Rangel-Frausto MS et al [81]which showed mortality ranging from 20-35% and study conducted by Greg S et al 2006 which showed case fatality increased linearly with age and age was an independent predictor of mortality.[82]

A study done by Angus DC et al showed that women had less age specific incidence and mortality rates compared to men. In this study out of 50 patients, among the 19 Non Survivors 5 were female(26.21 %) and 14 were male (73.68%).In this study mortaliy rate is higher in males than females. Among the 19 patients who died 7 (36.84%) had an infectious source in the lung. Other causes included localized infection in the form of cellulitis or abscess or an abdominal source of infection. Urinary tract infections were excluded from the study as it was an exclusion criteria of the study.

A study done by Angus DC et al [73] showed that 44% of the cause of mortality had a respiratory source of infection, 17.3 % had bacteremia from an unidentified source and 8.6 % had an abdominal source and 6.6 % had local wound as a source of infection.

Similar study done by dolin et al[83] showed that most common primary sources of infection resulting in sepsis are the lungs, the abdomen, and the urinary tract.Of the 19 patients who died 4 patients(8%) were immunocompromised.

Comparison of mortality percentage with other studies

Study	Ron Daniel et al[84]	Rangel frausto et al[81]	Russel et al	Present study
% male	35%	20 - 35%	20 – 35%	38%

7) APACHE II SCORE

In this study out of 50 patients APACHE II score ranged from 6 to 37 with a mean value of 19.82(SD±8.11). Out of 36 patients who had APACHE II score of more than 18.5, 15 patients died (55.55%), when compared to patients who had APACHE II score of less than 18.5, four patients died (17.39%)

The mean APACHE II score among the survivors was 16.35 with Standard Deviation of 6.78, when compared to the mean value of non survivors was 25.47 with Standard Deviation of 6.93 .As the P value was <0.0001, hence it was statistically significant.

8) URINE ACR 1(Albumin Creatinine Ratio):

Urine for ACR (Urine Albumin Creatinine Ratio) collected on admission (Urine ACR1) and within 24 hour of admission (Urine ACR2**).**In this study out of

50 patients Urine Micro Albumin Creatinine Ratio done on admission ranged 33 to 245 microgram/mg with mean value of 108.44 ± 55.05.Urine ACR1 differed significantly among survivors and non survivors. Patients who survived had mean ACR1 of 74.06 ± 20.83µg/mg and patients who died had mean ACR1 of 164.53 ± 46.61µg/mg.

ACR 1	**Gosling et al [77]**	**S Basu et al [74]**	**Present study**
Surviour	70.4	108	84
Non surviour	168.6	156.6	158
P value	0.0002	0.0004	0.0001

Out of 16 patients (32%) who had ACR value more than 109.5, all the 16 patients died.Out of 34 patients (68%) who had ACR value less than 109.5, three patients died (8.82%).There is statistically significant P value of < 0.0001 for survivor and non survivor.

9) URINE ACR 2 (Albumin Creatinine Ratio):

In this study out of 50 patients Urine Micro Albumin Creatinine Ratio done on admission ranged 15 to 221 microgram/mg with mean value of 88.38 ± 60.96. Out of 16 patients (32%) who had ACR 2 value more than 118.5, all the 16 patientsdied.Out of 34 patients (68%) who had ACR value less than 118.5, three

patients died (8.82%).Urine ACR 2 differed significantly among survivors and non survivors. Patients who survived had mean ACR2 of 45.81±17.92µg/mg and patients who died had mean ACR2 of 157.84±36.96µg/mg.There is statistically significant P value of < 0.0001 for survivor and non survivor.A study done by gosling et al showed that Urine ACR at 24 hours was 36.96 µg/mg among survivors and 156.64µg/mg among non- survivors with significant p value of 0.0002(Mann Whitney test).

Comparison of median Urine ACR2 with other studies ACR2:

ACR 2	**Gosling et al 23]**	**S Basu et al[31]**	**Present study**
Surviour	36.96	50.8	46
Non surviour	156.64	154	155
P value	0.0002	0.0004	0.0001

SUMMARY

Sepsis has very high morbidity and mortality, which leads to major healthcare burden in the world.Though there is far advancement in the therapeutic options, the mortality rate remains high due to the delay in the diagnosis because of lack of availability of reliable diagnostic methods. There is significant improvement in the outcome of the patients in early goal directed therapy in severe sepsis and septic shock.Potent activation of inflammatory cascade in sepsis leads to endothelial dysfunction and increase in systemic capillary permeablity.the endothelial injury and capillary leak in the glomerulus results in increased excreation of albumin in the urine. Microalbuminuria is defined as excretion of 30 – 300 mg of albumin per day in the urine. The presence of microalbuminuria occurs very early in the onset of inflammatory process. The microvascular effects of systemic inflammation can be monitored by serial measurement of microalbumin in urine. Microalbuminuria is better indicator than Acute Physiological and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Function Assesment score (SOFA score) in predicting vasopressor requirement and mortality.

This study was conducted at Institute of Internal Medicine, Madras Medical college and Rajev Gandhi Government General Hospital, Chennai to evaluate the degree of microalbuminuria in sepsis patients and whether it could predict

mortality in sepsis and also also to evaluate the corrulation of microalbuminuria and APACHE II Score.

After getting approval from ethical committee 50 patients presented with features of SIRS and suspected infection were included after fulfilling the exclutioncriteria.Urine for ACR was done on admission and at 24 hours of admission and APACHE II Score was calculated in the first 24 hours of admission. Patients presenting with features of SIRS and suspected infection were included in the study and after exclusion, a total of 50 patients were included in the study. Urine for ACR (Albumin and Creatinine Ratio) was done on admission (ACR1) and at 24 hours (ACR2) of admission and APACHE II score calculated.

1) Total 50 patients were included in the study, the mean age group of patients were 43.5 ± SD 15.8. Patients were distributed from age 16 to 85 years.

2) Out of 50 patients 19 patients were females and 31 patients were males. Male patients constituted 62% and females 38%.

3) 27 patients had all the 4 criteria of SIRS, and 19 patients had 3 criteria of SIRS and 4 patients had only 2 criteria of SIRS.

4) Mortality in this study was 38%. 31 patients died out of total 50 patients and the mortality was more among male patients (62%) than among female patients and age was an independent predictor of mortality with mortality increasing linearly with age.

5) APACHE II score ranged from 6 to 37. Mean APACHE II score among survivors were 16.35 and among non survivors were 25.47 Non survivors has a higher APACHE II score compared to survivors. P value was statistically significant with p of < 0.0001.

6) Mean Urine ACR 1 among survivors was 74.06 μg/mg and among non survivors164.53 and ACR 2 was 45.81 among survivors and 157.4 among non survivors.Both were statistically significant with p value of 0.0001

LIMITATIONS OF THE STUDY

1) Sample size is small.

2) Smoking and Hypertension etc ... could be independent cause of microalbuminuria.

3) Patients with urological causes of sepsis were not included in the study group.

4) Sepsis with pre-existing Chronic kidney disease could not be included in the study.

CONCLUSION

- Presence of significant microalbuminuria at admission and persistence of microalbuminuria at 24 hrs of admission correlated well with mortality as comparable to APACHE II score.

- Survival rate in patients with severe sepsis can be improved by early institution of intensive therapy .

- Microalbuminuria is an inexpensive rapid diagnostic as well as prognostic tool.

- Hence microalbuminuria can be used as dynamic marker of sepsis.

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STUDY OF MICROALBUMINURIA IN SEPSIS WITH REFERENCE TO APACHE II SCORE

Name : Patient ID No:

Age/Sex : Contact No:

Occupation: Address:

DOA:

DOD:

CHIEF COMPLAINTS:

☐ Fever ☐ Burning micturation

☐ Breathlessness ☐ swelling of legs/puffiness of Face/Abdominal distention

☐ Cough with expectoration ☐ Decreased urine output

☐ Chest pain ☐ Altered sensorium

☐ Yellowish discoloration of urine/eyes ☐Abdominal pain ☐ Seizures

☐☐

H/O PRESENTING COMPLAINTS:

☐FEVER:☐BREATHLESSNESS

Duration- Duration-

Low grade/High grade Sudden onset/Insidious onset

Continuous/Intermittent Progression

Chills/Rigor Grade-

Associated with Bleeding- Diurnal variation-

manifestations/Myalgia/Joint pain PND/Orthopnoea

Aggravating/Relieving factor

COUGH WITH/WITHOUTCHEST PAIN:

EXPECTORATION: Duration-

Duration- Site

Sudden onset/Insidious onset Sudden onset/Insidious onset

Colour of the sputum Type

Blood stained/Not Radiation

Amount/Smell Aggravating/Relieving factor

ABDOMINAL PAIN:BURNING MICTURATION

Duration- Duration

Site

Sudden onset/Insidious onset

Type **YELLOWISH DISCOLOURATION**

Radiation **OF URINE/EYES**

Aggravating/Relieving factor Duration

Associated with constipation/diarrhoea

SWELLING OF LEGS/PUFFINESSFACEDECREASED URINE OUTPUT /ABDOMINAL DISTENTION

Duration Duration

Onset Amount of urine output

Progression

ALTERED SENSORIUMHEAD ACHE

Duration Duration-

Sudden onset/Insidious onset Site

Type

Continuous/Intermittent

SEIZURES Aggravating/Relieving factor
No of episodes
Type
Duration of each episode Associated with
Post ictal confusion
Trauma

OTHERS

PAST HISTORY:
☐DM ☐Pulmonary TB☐ SHT☐ CAD/Heart disease☐ Kidney disease☐ CVA/TIA☐ Other Neurological disease
☐Surgeries☐Similar illness ☐OTHERS

TREATMENT H/O:
DrugsNative medicine
Others
OBTETRIC H/O:FAMILY H/O:
Pregnant – yes/no

PERSONAL HISTORY:
☐ Smoking ☐ Diet ☐ Sleep
☐ Alcohol intake ☐Substance abuse ☐ Bowel/Bladder

GENERAL EXAMINATION
Consciousness/orientation
Built/Nourishment
Pallor/Icterus/Cyanosis/Clubbing/Lymphadenopathy/Pedal edema
Skin rash/Skin ulcer
Pulse: ***GCS:*** ***E-*** ***V-*** ***M-***
BP: ***MAP:***
RR:
SpO_2:
FiO_2 **RS:**
Temperature:
Pupil
DEM
Neck stiffness

SYSTEMIC EXAMINATION:
CVS:P/A:

CNS:

PROVISIONAL DIAGNOSIS:

INVESTIGATIONS

CBC:
Total WBC count -
DC – P - L- E- B-
Hb -
PCV - **ECG**:
ESR -
Platelet count -

LFT: **CXR:**

Total bilirubin -
Direct -
Indirect -
SGOT - **USG ABDOMEN/KUB:**
SGPT -
ALP -
Total protein -
Albumin -
Globulin - **URINE C/S:**

RFT:

Random blood sugar-
Blood Urea -
Serum Creatinine -
Fasting blood sugar- **BLOOD C/S:**
Postprandial blood sugar-

SERUM ELECTROLITES:

Sodium -
Potassium - **OTHERS:**
Chloride -
Bicarbonate -

FiO_2 -
ABG: ***PaO_2*** -
PCO_2 -
pH -
A-aDO_2= [FiO_2 (713)-5/4(PCO_2)] - PaO_2
Urine microalbumin:creatinine ratio (ACR-1)-within 6 hours =
Urine microalbumin:creatinine ratio (ACR-2)-at 48 hours =

APACHE II SCORE:

A)

Temp(rectal) - Sr. Na -
MAP - Sr. K -
HR - Sr.creatinine-
RR - PCV -
Oxygenation - WBC -
Arterial pH - GCS -

A)Total =
B) Age points =
C) Chronic health points=

Total APACHE II SCORE=A+B+C=

Predicted mortality:

Urine microalbumin:creatinine ratio (ACR-1)-within 6 hours =
Urine microalbumin:creatinine ratio (ACR-2)-at 24 hours =

Treatment and observations:

Length of the hospital stay:
Duration of mechanical ventilation:
Outcome:
Comments:

INFORMATION SHEET

TITLE:"STUDY OF MICROALBUMINURIA IN SEPSIS WITH REFERENCE TO APACHE II SCORE"

NAME OF THE INVESTIGATOR: Dr.PRABAHARAN.U

STUDY CENTRE: Rajiv Gandhi Government General Hospital, Chennai-03.

NAME OF THE PARTICIPANT: AGE: SEX:

PURPOSE OF THE STUDY: The purpose of this study is to find out the correlation between the degree of microalbuminuria and severity of sepsis.

STUDY DESIGN: Observational study

STUDY PROCEDURE: We are selecting certain cases and if you are found eligible, after filling up the questionnaire and clinical examination along with routine blood investigations, blood samples will also be sent for some special investigations like arterial blood gas analysis and blood culture and sensitivity. Also two urine sample will be collected, one within 6 hours and another at 24 hours of admission for analysis to calculate urine albumin : creatinine ratio. You will also undergo ECG, chest x ray (if needed), USG KUB/Abdomen (if needed) and lumbar puncture and CSF analysis (if needed). These tests and special studies do not affect your final report or management.

POSSIBLE RISKS: No possible risk**s** by means of this study.

POSSIBLE BENEFITS:if we found the degree of microalbuminuria correlates with severity of sepsis we can use this simple test as a prognostic marker in sepsis.

CONFIDENTIALITY OF THE INFORMATION OBTAINED FROM THE PATIENT: The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

DECISION TO PARTICIPATE IN THE STUDY: Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

RESULT OF THE STUDY:

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of the patient attenders

Date:

Place: Signature of Investigator

PATIENT CONSENT FORM

Study Title	:	**“Study of microalbuminuria in sepsis with reference to APACHE II score”**
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Name of the patient	:	
Age/Sex	:	
Identification Number	:	

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor’s behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or wellbeing or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological and biochemical tests. ☐

Signature/thumb impression

Patient’s Name and Address:

Signature of Investigator

Study Investigator’s Name:

Dr.PRABAHARAN.U.

SL. NO	NAME	AGE(YEARS)	SEX	IP No	APACHE II SCORE																		SIRS				NO OF SIRS CRITERIA	DIAGNOSIS	OUTCOME
					ACUTE PHYSIOLOGY SCORE VARIABLES												TOTAL ACUTE PHYSIOLOGY SCORE	AGE POINTS	CHRONIC HEALTH POINTS	APACHE II SCORE	URINE ACR 1	URINE ACR 2							
					TEMPERATURE(RECTAL)	MEAN ARTERIAL PRESSURE	HEART RATE	RESPIRATORY RATE	OXYGENATION	ARTERIAL pH/SERUM BICARBONATE	SERUM SODIUM	SERUM POTTASSIUM	SERUM CREATININE	HEMATOCRIT	WBC	GCS (15-GCS)							FEVER	TACHYCARDIA	TACHYPNOEA	LEUCOCYTOSIS/LEUCOPENIA			
1	SAROJA	70	Female	65429	1	0	1	1	1	0	0	1	0	0	1	6	12	5	0	17	103	58	+	+	+	+	4	ACUTE MENINGOENCEPHALITIS	Survived
2	MAHALAKSHMI	20	Female	68050	1	0	2	3	3	3	1	1	0	0	0	4	18	0	0	18	107	104	+	+	+	+	4	SEPSIS,ARDS,MODS	Death
3	SELVARAJ	65	Male	68389	1	0	2	1	1	0	0	0	0	0	0	1	6	5	0	11	74	37	+	+	+	-	3	LEFT THIGH ABSCESS	Survived
4	VASANTHA	55	Female	68478	1	0	2	3	1	3	1	0	0	0	1	5	17	3	0	20	68	55	+	+	+	+	4	SHT,ACUTE MENINGOENCEPHALITIS	Survived
5	MANIMALA	38	Female	69286	0	2	2	3	1	2	0	1	0	1	0	3	15	0	5	20	86	53	-	+	+	-	2	B/L CYSTIC LUNG DISEASE,SEPSIS	Survived
6	KANNIAPPAN	40	Male	69963	1	4	3	3	3	4	1	1	1	1	0	12	34	0	0	34	224	201	+	+	+	-	3	SEPSIS,ARDS,MODS	Death
7	THIRUMURUGAN	32	Male	69970	1	2	2	3	3	2	2	0	1	0	0	4	20	0	5	25	170	155	+	+	+	+	4	RVD POSITIVE,B/L PNEUMONIA,SEPSIS	Death
8	SAVITHRI	55	Female	70024	1	2	2	2	1	2	1	0	1	1	0	1	14	3	0	17	62	53	+	+	+	-	3	LEFT LEG CELLULITIS,SEPSIS	Survived
9	SURYA NARAYANAVASAN	45	Male	71816	0	0	2	4	1	3	1	1	0	0	1	4	17	1	0	18	97	96	-	+	+	+	3	SCHIZOPHRENIA,ASPIRATION PNEUMONITIS,RESPIRATORY FAILURE	Death
10	SHANMUGA LAKSHMI	57	female	73082	1	4	2	3	3	3	1	1	1	1	0	4	24	3	0	27	85	58	+	+	+	+	4	SEPSIS,ARDS,RESPIRATORY FAILURE	Survived
11	VISWANATHAN	85	Male	73517	0	4	3	3	2	4	3	1	1	1	0	6	28	6	0	34	222	177	-	+	+	+	3	ACUTE MENINGO ENCEPHALITIS/SEPSIS/SEPTIC SHOCK	Death
12	VISHNU PRIYA	17	Male	73566	1	0	0	3	1	2	0	0	0	0	0	4	11	0	0	11	55	34	+	+	+	-	3	ATAXIA TELENGECTATIA,LEFT LOWER LOBE CONSOLIDATION	Survived
13	PITCHAI RAJ	49	Male	73920	1	2	2	3	2	1	1		0	0	1	3	16	2	0	18	99	123	+	+	+	+	4	RUPTURED LIVER ABSCESS,SEPSIS	Death
14	GAJENDRAN	52	Male	75912	0	4	3	4	3	3	2	2	1	1	0	6	29	2	0	31	133	185	-	+	+	-	2	ASPIRATION PNEUMONITIS,SEPTIC SHOCK,RESPIRATORY FAILURE	Death
15	JEYAMMAL	60	Female	76969	1	4	2	1	3	0	0	0	1	1	2	3	18	3	0	21	47	46	+	+	+	+	4	RT NECROTISING PNEUMONIA,SEPTIC SHOCK	Survived
16	SUBRAMIANI	45	Male	77323	1	0	2	3	2	3	1	1	0	0	0	4	17	2	0	19	85	33	+	+	+	+	4	CAD,RIGHT LOWER LOBE PNEUMINIA	Survived
17	DHAMODHARAN	56	Male	80278	1	0	2	2	1	3	1	1	0	1	0	7	19	3	0	22	95	72	+	+	+	+	4	ACUTE MENINGOENCEPHALITIS	Survived
18	SUMITHRA	21	Female	80318	1	2	2	4	1	2	1	0	1	0	1	4	19	0	0	19	160	132	+	+	+	+	4	SEPSIS,MODS	Death
19	KASI	60	Male	80497	0	4	3	4	3	3	1	1	0	1	0	7	27	3	5	35	225	208	-	+	+	-	2	SEPSIS,ARDS	Death
20	SENTHAMARAI	50	Female	81441	1	2	2	1	0	0	0	0	0	0	0	1	7	2	0	9	42	18	+	+	+	+	4	LT LL CELLULITIS,SEPSIS	Survived
21	MAHESHWARI	45	Female	81764	1	2	2	3	3	2	0	0	0	1	1	3	18	2	0	20	84	58	+	+	+	+	4	RHD,PNEUMONIA,SEPSIS	Survived
22	VAITHESHWARAN	32	Male	81857	1	0	3	3	1	2	0	0	0	0	0	4	14	0	5	19	149	114	+	+	+	-	3	RVD ,ASPIRATION PNEUMONITIS,SEPSIS	Death
23	CHINNARAJ	24	Male	82756	1	4	2	3	1	4	1	1	1	1	2	5	26	0	0	26	55	64	+	+	+	+	4	RUPTURED LIVER ABSCESS,SEPSIS	Survived

24	GRACE	26	Female	82774	1	2	2	3	3	2	1	0	0	0	0	7	21	0	0	21	112	143	+	+	+	-	3	SEPSIS,ARDS,RESPIRATORY FAILURE	Death
25	CHANDRASEKAR	51	Male	84658	0	0	2	1	3	0	0	0	0	0	0	1	7	2	5	14	92	33	-	+	+	+	3	RIGHT LOWER LOBE BRONCHECTASIS/SEPSIS	Survived
26	ANU	28	Female	84726	1	4	2	2	1	3	2	1	1	1	0	4	22	0	5	27	76	68	+	+	+	-	3	RVD POSITIVE,SEPSIS	Survived
27	VENKADESAN	45	Male	84732	1	2	2	3	3	1	1	0	0	0	1	2	16	2	0	18	88	48	+	+	+	+	4	RIGHT LOWER LOBE PNEUMONIA	Survived
28	VIVEK	18	Male	84800	1	2	0	1	0	0	0	0	0	1	1	0	6	0	0	6	62	30	+	+	+	-	3	SEPSIS	Survived
29	DEVARAJ	53	Male	84851	1	0	2	1	0	0	0	0	1	0	0	4	9	2	0	11	35	44	+	+	+	+	4	SHT,ACUTE MENINGOENCEPHALITIS	Survived
30	MOHAMED ALI	50	Male	84954	0	2	2	1	1	0	0	0	0	0	0	1	7	2	0	9	87	27	-	+	+	-	2	RIGHT MIDDLE LOBE CONSOLIDATION	Survived
31	CHINNATHAMBI	39	Male	85354	1	2	2	3	1	2	2	1	1	1	0	2	18	0	0	18	33	52	+	+	+	-	3	CHRONIC ALCOHOLIC,SEPSIS,SEPTIC ENCEPHALOPATHY	Survived
32	SHAHERTHA BEGAM	50	Female	85594	1	4	2	4	2	1	0	1	1	1	0	4	21	2	5	28	167	162	+	+	+	+	4	COPD,SECONDARY INFECTION,RESPIRATORY FAILURE,SEPTIC SHOCK	Death
33	GAJALAKSHMI	16	Female	85739	1	0	0	1	0	0	0	0	0	0	1	3	6	0	0	6	71	32	+	+	+	+	4	ACUTE MENINGO ENCEPHALITIS	Survived
34	SABASTEIN	56	Male	86659	1	2	2	3	2	2	0	1	0	0	0	4	17	3	0	20	156	150	+	+	+	+	4	SHT,OLD CVA,LIVER ABSCESS,SEPSIS	Death
35	RAJ	39	Male	87001	1	0	2	3	1	2	2	1	1	1	0	4	18	0	5	23	158	155	+	+	+	-	3	DCLD,SEPSIS	Death
36	SULTHAN BASHA	30	Male	87730	1	4	2	2	2	3	2	0	0	1	0	10	27	0	0	27	158	158	+	+	+	+	4	CSOM,CEREBELLAR ABSCESS	Death
37	RAMALINGAM	60	Male	87830	1	4	2	3	1	2	0	0	1	1	0	2	17	3	5	25	92	84	+	+	+	+	4	DCLD,LEFTLOWER LOBE CONSOLIDATION	Survived
38	MUNUSAMY	53	Male	87835	1	2	2	1	0	0	0	0	0	0	1	3	10	2	0	12	89	35	+	+	+	+	4	ACUTE MENINGOENCEPHALITIS	Survived
39	VAIRAM	35	Male	87943	1	0	2	3	1	1	1	0	0	0	0	9	18	0	0	18	179	142	+	+	+	-	3	CHRONIC ALCOHOLIC,ACUTE MENINGOENCEPHALITIS	Death
40	THIYAGARAJAN	45	Male	88800	1	0	2	1	0	0	0	0	0	0	0	3	7	2	0	9	61	23	+	+	+	-	3	ACUTE MENINGOENCEPHALITIS	Survived
41	MADURAI	75	Male	88820	1	4	2	3	1	2	0	0	1	1	0	2	17	6	0	23	102	68	+	+	+	+	4	LIVER ABSCESS	Survived
42	PALANI	41	Male	88879	1	4	2	1	0	0	0	0	1	1	1	4	15	0	0	15	100	46	+	+	+	+	4	SHT,ACUTE NECROTISING PANCREATITIS,ASPIRATION PNEUMONITIS	Survived
43	SRIDEVI	35	Female	88906	1	0	2	3	0	3	0	1	0	0	0	3	13	0	0	13	99	36	+	+	+	-	3	ACUTE MENINGOENCEPHALITIS	Survived
44	DILLI BASKAR	40	Male	89353	1	2	2	4	3	2	2	1	0	1	0	6	24	0	0	24	133	152	+	+	+	+	4	CHRONIC ALCOHOLIC,NECROTISING PNEUMONIA,SEPSIS	Death
45	ABDUL KAPOOR	55	Male	90420	1	2	2	2	3	4	0	2	0	1	2	3	22	3	5	30	88	80	+	+	+	+	4	COPD,RIGHT LOWER LOBE PNEUMONIA,SEPSIS	Survived
46	SURESH	32	Male	90541	1	4	2	4	2	3	2	1	1	2	0	8	30	0	5	35	232	221	+	+	+	-	3	DCLD,PHT,B/L LL CELLULITIS,SEPSIS	Death
47	ANJALA	50	Female	90587	1	2	2	3	0	1	0	0	0	0	1	3	13	2	0	15	85	34	+	+	+	+	4	ACUTE MENINGOENCEPHALITIS	Survived
48	KARTHIKA	21	Female	91431	1	2	2	2	0	1	0	1	0	0	0	1	10	0	0	10	44	26	+	+	+	-	3	PERI ANAL ABSCESS,SEPSIS	Survived
49	DEVAKI	17	Female	91589	1	0	0	1	0	0	0	0	0	0	0	4	6	0	0	6	51	15	+	+	+	-	3	ACUTE MENINGOENCEPHALITIS	Survived
50	NIRMALA	42	Female	92150	1	4	3	4	3	3	2	2	1	2	1	6	32	0	5	37	245	221	+	+	+	+	4	DCLD,PHT,SEPSIS,REFRACTORY SEPTIC SHOCK	Death

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Prabaharan .U,
Post Graduate in MD Internal Medicine,
Madras Medical College,
Chennai – 600003.

Dear Dr. Prabaharan .U,

The Institutional Ethics Committee has considered your request and approved your study titled **"Study of Microalbuminuria in Sepsis with reference to APACHE II score"** No. 43072014.

The following members of Ethics Committee were present in the meeting held on 01.07.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C. Rajendran, M.D.	-- Chairperson
2.	Dr. R. Vimala, M.D., Dean, MMC, Ch-3.	-- Deputy Chair Person
3.	Prof. Kalaiselvi, MD., Vice-Principal, MMC, Ch-3	-- Member Secretary
4.	Prof. Nandhini, M.D. Inst. of Pharmacology, MMC, Ch-3.	-- Member
5.	Dr. G. Muralidharan, Director Incharge , Inst. of Surgery	-- Member
6.	Prof. Md Ali, MD., DM., Prof & HOD of MGE, MMC, Ch-3.	-- Member
7.	Prof. Ramadevi, Director i/c, Biochemistry, MMC,Ch-3.	-- Member
8.	Prof. Saraswathy, MD., Director, Pathology, MMC, Ch-3.	-- Member
9.	Prof. Tito, Director, i/c. Inst. of Internal Medicine, MMC	-- Member
10.	Thiru. Rameshkumar, Administrative Officer	-- Lay Person
11.	Thiru. S. Govindasamy, BABL, High Court, Chennai-1.	-- Lawyer
12.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

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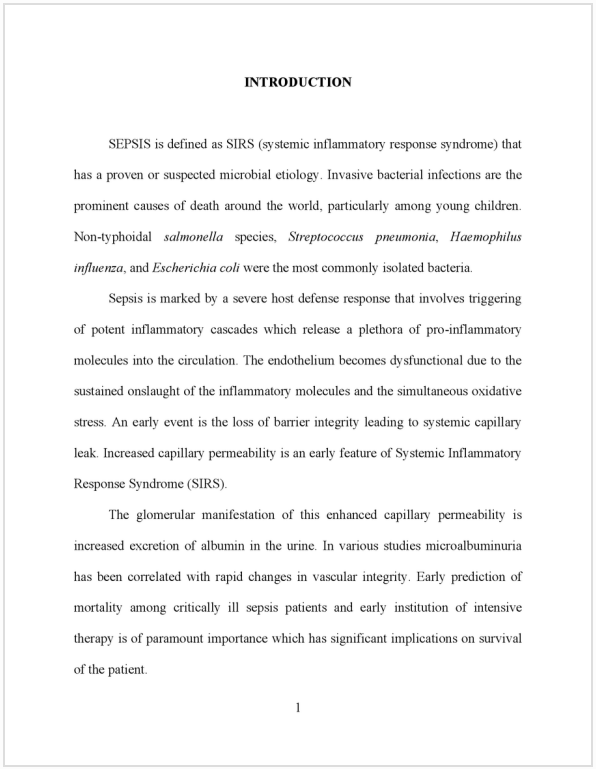

INTRODUCTION

SEPSIS is defined as SIRS (systemic inflammatory response syndrome) that has a proven or suspected microbial etiology. Invasive bacterial infections are the prominent causes of death around the world, particularly among young children. Non-typhoidal *salmonella* species, *Streptococcus pneumonia*, *Haemophilus influenza*, and *Escherichia coli* were the most commonly isolated bacteria.

Sepsis is marked by a severe host defense response that involves triggering of potent inflammatory cascades which release a plethora of pro-inflammatory molecules into the circulation. The endothelium becomes dysfunctional due to the sustained onslaught of the inflammatory molecules and the simultaneous oxidative stress. An early event is the loss of barrier integrity leading to systemic capillary leak. Increased capillary permeability is an early feature of Systemic Inflammatory Response Syndrome (SIRS).

The glomerular manifestation of this enhanced capillary permeability is increased excretion of albumin in the urine. In various studies microalbuminuria has been correlated with rapid changes in vascular integrity. Early prediction of mortality among critically ill sepsis patients and early institution of intensive therapy is of paramount importance which has significant implications on survival of the patient.

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